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High neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predict poor survival in rectal cancer patients receiving neoadjuvant concurrent chemoradiotherapy

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Abstract

This study explored the prognostic value of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in rectal cancer patients receiving neoadjuvant concurrent chemoradiotherapy (CCRT).

Between January 2006 and December 2016, 184 patients with newly-diagnosed rectal cancer receiving neoadjuvant CCRT were enrolled. Risk of overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method and Cox proportional hazard models. Stratified survival analyses were also performed between post-neoadjuvant pathological (yp) stage.

The mean follow-up time was 72.73±36.82 months. High- and low-NLR patients differed significantly in both 5-year DFS ($P=.026$) and OS ($P=.016$). High- and low-PLR patients differed significantly in 5-year DFS ($P=.011$) but not OS ($P=.185$). Multivariate analyses revealed worse 5-year DFS (adjusted HR [aHR]=2.8; 95% CI: 1.473–5.41; $P=.002$) and 5-year OS (aHR=1.871; 95%CI: 1.029–3.4; $P=.04$) in the high-NLR group after adjusting for covariates. After adjustments, the high-PLR group had inferior 5-year DFS (aHR=2.274; 95%CI: 1.473–5.419; $P=.038$) but not 5-year OS (aHR=1.156; 95%CI: 0.650–2.056; $P=.622$). Further stratified analysis indicated that yp stage II and III patients with high NLR had worse 5-year DFS (aHR=2.334; 95% CI: 1.158–4.725; $P=.018$) and OS (aHR=2.226; 95% CI: 1.165–4.251; $P=.015$). Additionally, yp stage II and III patients with high PLR had inferior 5-year DFS (aHR=2.012; 95% CI: 1.049–3.861; $P=.036$).

Pre-CCRT NLR and PLR are independent prognostic factors for rectal cancer patients and could be used as a potential biomarker to identify high-risk patients for more intense treatment and care.

Abbreviations: CCRT = concurrent chemoradiotherapy, CRC = colorectal cancer, CRM = circumferential resection margin, DFS = disease free-survival, LVI = lymphovascular invasion, NCCN = National Cancer Information Network, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PLR = platelet-to-lymphocyte ratio, PNI = perineural invasion, TME = total mesorectal excision, TRG = tumor regression grade.

Keywords: neoadjuvant concurrent chemoradiotherapy, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, rectal cancer, survival

Editor: Sergio Huerta.

WCT and CCY these authors contributed equally to this work.

Compliance with Ethical Standards

The authors received no financial support for the research, authorship, and/or publication of this article.

This study was supported by grants from the Health and Welfare surcharge of tobacco products (MOHW109-TDU-B-212–134020, WanFang Hospital, Chi-Mei Medical Center, and Hualien Tzu-Chi Hospital Joing Cancer Center Grant-Focus on Colon Cancer Research); Chi-Mei Medical Center [CMFHR108105 and CMFHR10828].

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Ke TM, Lin LC, Huang CC, Chien YW, Ting WC, Yang CC. High neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predict poor survival in rectal cancer patients receiving neoadjuvant concurrent chemoradiotherapy. Medicine 2020;99:17(e19877).

Received: 28 December 2019 / Received in final form: 10 March 2020 / Accepted: 11 March 2020

http://dx.doi.org/10.1097/MD.0000000000019877

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related death worldwide.[1] Rectal cancer accounts for 30% to 35% of CRCs, and approximately 50% of rectal cancers are diagnosed at the locally advanced stage.[2] With advances in the treatment of neoadjuvant concurrent chemoradiotherapy (CCRT),[3] followed by total mesorectal excision (TME), outcomes have improved dramatically in recent decades. However, significant differences in survival still exist between post-treatment groups. Useful and practical prognostic biomarkers obtained before treatment are anticipated to forecast the outcome after mainstream treatment. Such biomarkers will help in planning strategies for customized postoperative adjuvant therapy.

Inflammation-driven markers play a crucial role in tumorigenesis and tumor progression.[4] More evidences had reported systemic inflammation-based biomarkers could be used to predict tumor behavior.[5] Two convenient and economic measures of systemic inflammation, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been advocated to reflect the interaction between inflammation and host immune status, making them potential prognostic factors for various types of cancers.[6] Increased NLR has been advocated to be an independent prognostic factor for poor survival outcomes in pancreatic cancer, CRC, and gastric cancer.[7–9] Elevated PLR has also been reported to be associated with poor prognosis in different cancers.[10,11] Although previous studies used systemic inflammation response such as NLR and PLR to assess the prognostic ability in rectal patients undergoing neoadjuvant CCRT, the results remain inconclusive.[12,13] Thus, this study aimed to investigate the prognostic value of pre-CCRT NLR and PLR in patients with rectal cancer post neoadjuvant CCRT.

2. Methods and materials

2.1. Ethics statement

Written informed consent was not required for this observational study as it was a retrospective medical record review. The study protocol was approved by the Ethics Committee of the Institutional Review Board of Chi Mei Medical Center (IRB: CMFHR10707–012).

2.2. Patient demographics and database

The data for this study were collected from the Cancer Registry Dataset of Chi-Mei Medical Center between January 1, 2006 and December 31, 2016. Electronic medical records and the Cancer Registry Dataset were retrospectively reviewed. All patients were regularly monitored after diagnosis until death or last follow up. A total of 184 patients with rectal cancer who underwent neoadjuvant CCRT followed by TME in accordance with National Comprehensive Cancer Network (NCCN) guidelines were identified in this study. Exclusion criteria included the following: previous cancer history, aged <18 years, incomplete patient data or being coded as receiving palliative care. All patients received long course radiation therapy at the dose of 45 to 50 Gray (Gy) in 25 to 28 fractions to the pelvis by NCCN recommendation, and radiation techniques were completed by intensity modulated radiation therapy, arc therapy or tomotherapy. All patients received pre-operation chemotherapy in 6 courses of 5-fluorouracil-based regimens and post-operation chemotherapy in 6 courses of FOLFOX or 5-FU/leucovorin or capcitabine regimens.

Our Cancer Registry Dataset provided the following clinicopathological characteristics: date of diagnosis, age, gender, clinical stage and pathological stage according to the American Joint Committee on Cancer (AJCC) cancer staging (7th edition), pathologic tumor grade, perineural invasion (PNI), lymphovascular invasion (LVI), circumferential resection margin (CRM), tumor regression grade (TRG), NLR and PLR. TRG was done a standard 5-point scale as initially described by Dworak et al.[14] NLR was determined by the neutrophil count divided by the total lymphocyte count. PLR was defined as the absolute platelet count divided by the total lymphocyte count. NLR and PLR values were determined based on complete blood count obtained within 2 weeks before neoadjuvant CCRT. Patients were excluded from the study if they had any acute infection.

2.3. Statistical analysis

All statistical operations were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY). All statistical significance levels were set as 2-sided, with $P < .05$. The primary endpoint was disease free-survival (DFS), defined as the time from the day of disease diagnosis until the day of disease failure. The secondary endpoint was overall survival (OS), defined as the time from the day of disease diagnosis until the date of death. The cut-off value of NLR and PLR were set as the mean value of each. The 5-year DFS and OS were described using the Kaplan-Meier method, and the differences were compared using log-rank statistics. Univariate and multivariate Cox regression models were used to evaluate the effect of NLR and PLR on 5-year DFS and 5-year OS. Stratified survival analyses were also performed between different yp stages.

3. Results

The demographic, clinical and pathological characteristics of this study are displayed in Table 1. A total of 184 patients were identified, 121 (65.8%) male and 63 (34.2%) female. The mean follow-up time was 72.73 ± 36.82 months. The mean age of all patients at diagnosis was 63.2 ± 11.7 years, with 97 (52.7%) patients $\leq$65 years and 87 (47.3%) patients >65 years. The mean NLR and PLR values pre-CCRT were 3.5 and 187.9, respectively. In all, 146 (79.3%) patients had pre-CCRT NLR $\leq$3.5 and 38 (20.7%) patients had pre-CCRT NLR > 3.5. Pre-CCRT PLR was $\leq$188 in 121 (70.1%) patients and >188 in 25 (29.9%) patients. According to clinical stage, 49 (26.6%) patients were at c stage I, 56 (30.4%) at c stage II and 79 (42.9%) at c stage III. In terms of yp stage, 23 (12.5%) patients were at yp stage 0, 54 (29.3%) at yp stage I, 43 (24.3%) at yp stage II and 64 (34.8%) at yp stage III. Additionally, 23 (12.5%) patients were TRG 4, which was compatible to the proportion of those with complete response (yp stage 0). Moderately differentiated tumor grade (grade 2) was found in 136 (73.9%) patients. In terms of other pathological features, 168 (91.3%) patients had negative PNI, 160 (87%) patients had negative LVI and 153 (95.7%) patients had negative CRM. The relationship between NLR or PLR status and these clinicopathological factors were also analyzed. However, there were no statistically significant difference between NLR or PLR status and clinicopathological factors, such as c stage, yp stage, LN metastasis, Grade, PNI, LVI, CRM, TRG and blood marker

Table 1

Clinico-pathological characteristics of the patients (n = 184).

Variable	n	(%)
Age, yr mean (SD)	63.17	(11.7)
Age		
≤65	97	(52.7)
>65	87	(47.3)
Gender		
Male	121	(65.8)
Female	63	(34.2)
c Stage		
I	49	(26.6)
II	56	(30.4)
III	79	(42.9)
yp stage		
0	23	(12.5)
I	54	(29.3)
II	43	(23.4)
III	64	(34.8)
Grade		
1	20	(10.9)
2	136	(73.9)
3	21	(11.4)
4	7	(3.8)
PNI		
Negative	168	(91.3)
Positive	16	(8.7)
LVI		
Negative	160	(87)
Positive	24	(13)
CRM		
Negative	153	(95.7)
Close/Positive	7	(4.3)
Pre-CCRT NLR		
≤3.5	146	(79.3)
>3.5	38	(20.7)
Pre-CCRT PLR		
≤188	121	(70.1)
>188	25	(29.9)
TRG		
0–1	31	(16.8)
2–3	130	(70.7)
4	23	(12.5)

All values are expressed as number (percentage) unless otherwise noted.
CRM = circumferential resection margin, LVI = lymphovascular invasion, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PNI = perineural invasion, TRG = tumor regression grade.

CEA (supplementary table 1, http://links.lww.com/MD/E82 and 2, http://links.lww.com/MD/E83).

Kaplan-Meier survival curves were generated to compare 5-year DFS and 5-year OS. As shown in Figures 1 and 2, the 5-year DFS differed significantly between those with pre-CCRT NLR >3.5 and ≤3.5; and between those with pre-CCRT PLR >188 and ≤188 as well. Log-rank tests showed that groups with pre-CCRT NLR >3.5 and PLR >188 had significantly worse 5-year DFS than those with pre-CCRT NLR ≤3.5 and pre-CCRT PLR ≤188 ($P = .011$ and $P = .011$, respectively). Figure 3 shows that the 5-year OS differed significantly between those with pre-CCRT NLR >3.5 and ≤3.5; however, 5-year OS did not differ significantly between those with pre-CCRT PLR >188 and ≤188 (Fig. 4). Log-rank tests showed that those with pre-CCRT NLR >3.5 had significantly worse 5-year OS than those with pre-CCRT NLR ≤3.5 ($P = .016$).

In univariate analysis, Grade 3 (p = .005, HR = 2.209, 95% CI: 1.182–4.129), PNI ($P = .015$, HR = 2.587, 95% CI: 1.207–5.543), LVI ($P = .005$, HR = 2.507, 95% CI: 1.313–4.788), yp stage III ($P = .005$, HR = 2.083, 95% CI: .802–5.41), TRG 4 ($P = .005$, HR = 0.276, 95% CI: 0.092–0.825), pre-CCRT NLR >3.5 ($P = .029$, HR = 1.957, 95% CI: 1.073–3.57) and pre-CCRT PLR >188 ($P = .013$, HR = 2.019, 95% CI: 1.163–3.503) were significant prognostic factors for poor 5-year DFS. In multivariate analysis, Grade 3 ($P = .005$, adjusted hazard ratio [aHR] = 2.233, 95% CI: 1.161–4.294), LVI ($P = .046$, aHR = 2.151, 95% CI: 1.014–4.563), yp stage III ($P = .019$, aHR = 1.421, 95% CI: 0.524–3.852), TRG 4 ($P = .002$, aHR = 0.054, 95% CI: 0.005–0.606), pre-CCRT NLR >3.5 ($P = .002$, aHR = 2.825, 95% CI: 1.473–5.419) and pre-CCRT PLR >188 ($P = .038$, aHR = 2.274, 95% CI: 1.047–4.937) all remained as independent prognostic factors for 5-year DFS (Table 2).

Furthermore, univariate analysis showed that PNI ($P = .000$, HR = 3.378, 95% CI: 1.927–5.921) and pre-CCRT NLR >3.5 ($P = .017$, HR = 1.748, 95% CI: 1.105–2.765) were significant risk factors for 5-year OS. Multivariate analysis indicated that Grade 3 ($P = .04$, adjusted hazard ratio [aHR] = 2.353, 95% CI: 0.960–5.768), PNI ($P = .001$, aHR = 3.416, 95% CI: 1.693–6.895) and pre-CCRT NLR >3.5 ($P = .04$, aHR = 1.871, 95% CI: 1.029–3.4) remained as independent prognostic factors for 5-year OS (Table 3).

In stratified analysis according to yp stage, only yp stage II-III patients with NLR >3.5 had significantly worse 5-year DFS ($P = .018$; aHR = 2.334; 95% CI: 1.158–4.725) and 5-year OS ($P = .015$; aHR = 2.226; 95% CI: 1.165–4.251), after adjustments. In addition, only yp stage II-III patients with PLR >3.5 had worse 5-year DFS ($P = .036$; aHR = 2.012, 95% CI: 1.049–3.861), after adjustments (Table 4).

4. Discussion

This observational study evaluated the effects of pre-CCRT NLR and PLR to predict survival in patients with neoadjuvant rectal cancer. Our results found that high NLR patients had significantly inferior 5-year DFS and OS, as compared with low NLR patients, and high PLR patients exhibited significantly poorer 5-year DFS than low PLR patients, even after adjusting for all demographic and clinico-pathologic factors. Stratified analysis showed that patients with elevated NLR with yp stage II-III had significantly poorer 5-year DFS and OS than those with yp stage 0 to I; correspondingly, patients with elevated PLR with yp stage II to III had also had significantly poorer 5-year DFS than those with yp stage 0 to I.

The strengths of this study are as follows. First, patients in our study were treated at a single institution and received neoadjuvant CCRT as routine clinical practice and all regimens were based on NCCN recommendations. Thus, variations in treatment regimen and technique were not likely to have biased results between patients. Furthermore, our database provided crucial information about predisposing factors that could influence survival (ie, age, stage, grade, PNI, LVI, CRM and TRG), thus allowing for an in-depth evaluation of the impact of these factors on outcomes. Third, included were only rectal cancer patients with neoadjuvant CCRT followed by TME. These inclusion criteria facilitated a study under homogeneous patient and treatment conditions. Hence, our conclusion is more specific than that of Ian et al.,[15] which included patients diagnosed with all gastrointestinal malignancies under heterogenetic treatment.

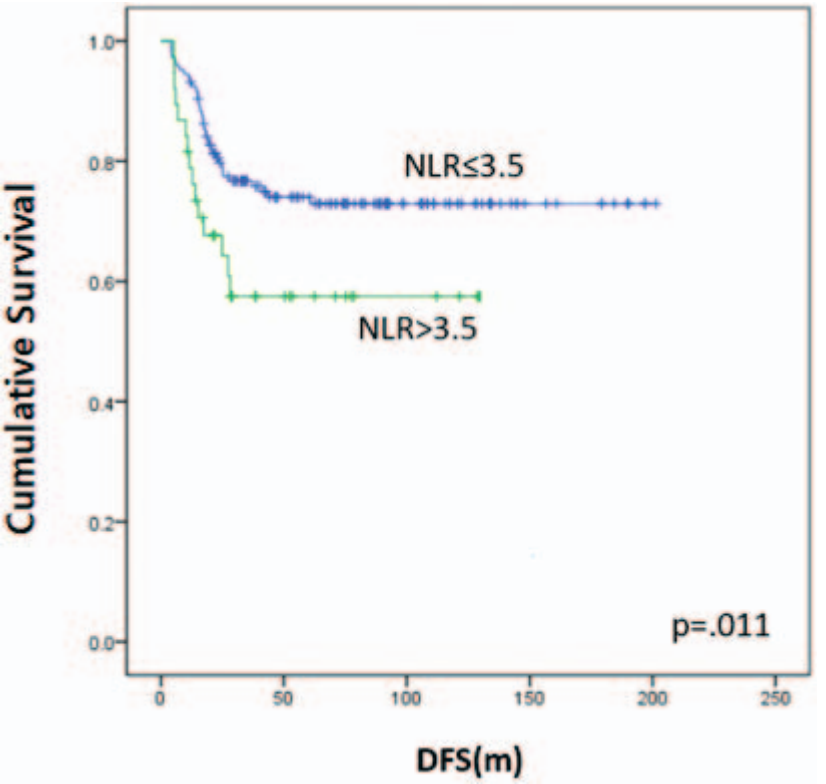

Figure 1. Kaplan-Meier plot of 5-year disease free survival (DFS) between NLR ≤3.5 and >3.5. NLR = neutrophil to lymphocyte ratio.

Finally, the use of stratification analysis made survival prediction more precise than in other studies. Therefore, pre-CCRT NLR and PLR can be recommended as important independent prognostic biomarkers for neoadjuvant rectal cancer.

The association of high NLR and PLR with poor outcomes has been explored before.[8,9,16] Although the precise mechanisms remain unknown, current consensus is that the hematological markers NLR and PLR may well reflect the host immune activity

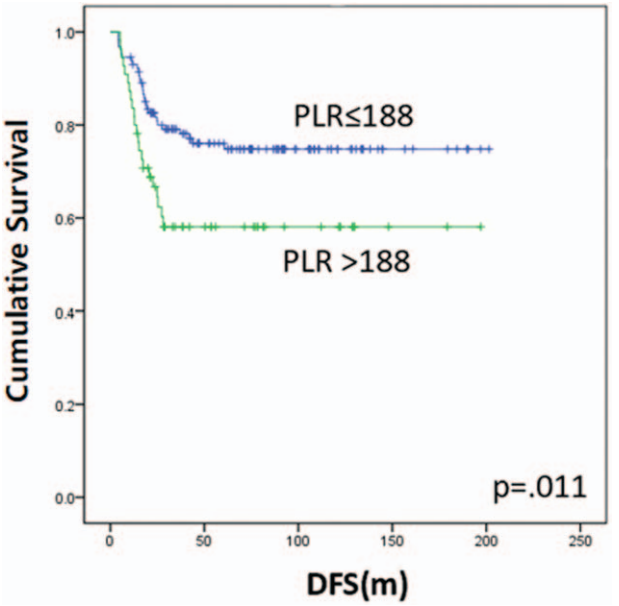

Figure 2. Kaplan-Meier plot of 5-year disease free survival (DFS) between PLR ≤188 and >188. PLR = platelet to lymphocyte ratio.

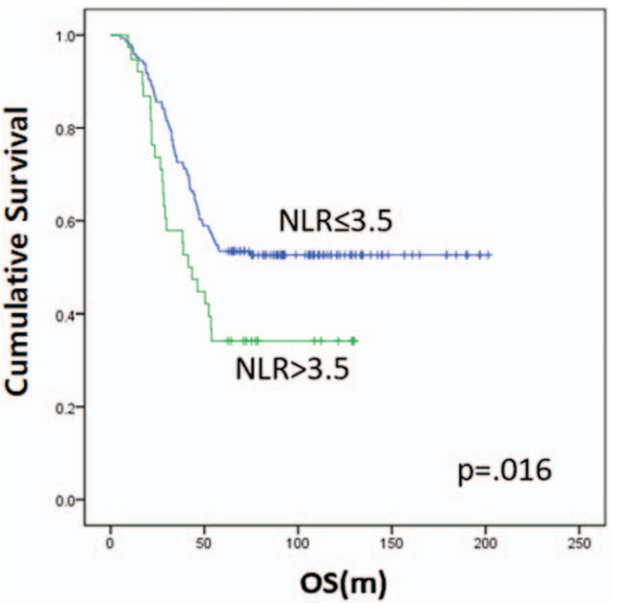

Figure 3. Kaplan-Meier plot of 5-year overall survival (OS) between NLR ≤3.5 and >3.5. NLR = neutrophil to lymphocyte ratio.

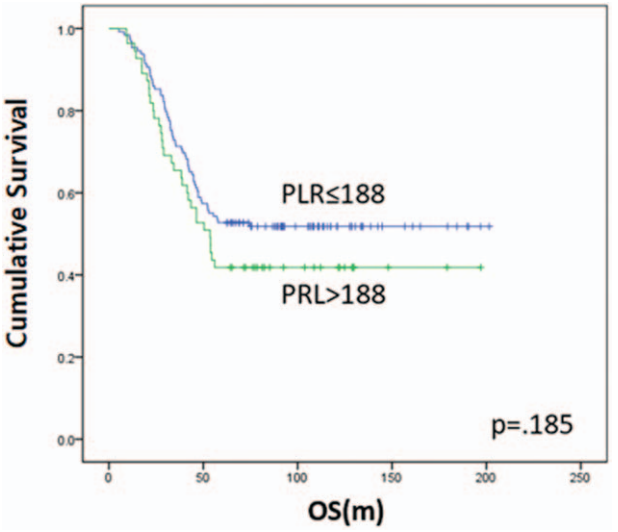

Figure 4. Kaplan-Meier plot of 5-year overall survival (OS) between PLR ≤188 and >188. PLR = platelet to lymphocyte ratio.

which is related to cancer progression.[17] Generally, neutrophils are considered to not only release cytokines, chemokines and granule proteins in building a favorable microenvironment for tumor progression, but they also act directly in carcinogenesis, assisting in metastasis by suppressing peripheral leukocyte activation.[18] In contrast, lymphocytes play a dominant role in restraining tumor growth.[19] Therefore, elevated NLR can stimulate a favorable tumor micro-environment which promotes vigorous tumor growth.[20,21] Platelets are thought to take part in tumor progression by regulating neo-angiogenesis and helping circulating tumor cells escape immune surveillance.[22,23] Thus, elevated PLR is assumed to be associated with tumor metastasis.

Numerous published meta-analyses have confirmed that a high NLR and a high PLR are both significant prognostic factors for poor outcomes in locally advanced and metastatic colorectal cancer (CRC).[24–26] Haowen et al[24] performed a meta-analysis of 8 studies including data from 1685 patients with CRC and liver metastasis; the results showed that elevated pretreatment NLR was significantly related to poor OS (HR = 2.17, 95% CI: 1.82–2.58) and recurrence-free survival (HR = 1.96, 95% CI: 1.64–2.35). George et al,[26] in a pooled analysis of 13 studies with 4,056 CRC patients, showed that a high pretreatment NLR

Table 2

Univariate and multivariate analyses of Pre-CCRT NLR and PLR for 5-yr disease free survival.

	Univariate DFS			Multivariate DFS*		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Pre-CCRT NLR						
≤3.5	Ref		.029	Ref		.002
>3.5	1.957	(1.073–3.570)		2.825	(1.473–5.419)	
Pre-CCRT PLR						
≤188	Ref		.013	Ref		.038
>188	2.019	(1.163–3.503)		2.274	(1.047–4.937)	
Age						
≤65	Ref		.391	Ref		.788
>65	0.786	(0.453–1.363)		0.921	(0.503–1.68)	
Gender						
Male	Ref		.470	Ref		.360
Female	1.229	(0.703–2.148)		1.323	(0.727–2.408)	
Grade						
1	Ref		.005	Ref		.005
2	0.927	(0.517–1.490)		0.984	(0.597–1.622)	
3	2.209	(1.182–4.129)		2.233	(1.161–4.294)	
4	1.394	(0.588–3.304)		2.130	(0.767–5.919)	
PNI						
Negative	Ref		.015	Ref		.114
Positive	2.587	(1.207–5.543)		2.026	(0.844–4.865)	
LVI						
Negative	Ref		.005	Ref		.046
Positive	2.507	(1.313–4.788)		2.151	(1.014–4.563)	
CRM						
Negative	Ref		.442	Ref		.083
Close/Positive	0.460	(0.062–3.332)		0.155	(0.019–1.275)	
yp Stage						
0	Ref		.005	Ref		.019
I	0.394	(0.114–1.360)		0.292	(0.083–1.032)	
II	1.727	(0.627–4.752)		1.207	(0.427–3.417)	
III	2.083	(0.802–5.410)		1.421	(0.524–3.852)	
TRG						
0–1	Ref		.005	Ref		.002
2–3	0.405	(0.222–0.739)		0.348	(0.180–0.672)	
4	0.276	(0.092–0.825)		0.054	(0.005–0.606)	

CI = confidence interval, CRM = circumferential resection margin, DFS = disease free survival, HR = hazard ratio, LVI = lymphovascular invasion, NLR = neutrophil to lymphocyte ratio, PLR = platelet to lymphocyte ratio, PNI = perineural invasion, TRG = tumor regression grade.

* Adjusted for age, gender, grade, PNI, LVI, CRM, yp stage, and TRG.

Table 3

Univariate and multivariate analyses of Pre-CCRT NLR and PLR for 5-yr overall survival.

	Univariate 5-year OS			Multivariate 5-yr OS*		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
Pre-CCRT NLR						
≤3.5	Ref		.017	Ref		.040
>3.5	1.748	(1.105–2.765)		1.871	(1.029–3.400)	
Pre-CCRT PLR						
≤188	Ref		.187	Ref		.622
>188	1.333	(0.870–2.043)		1.156	(0.650–2.056)	
Age						
≤65	Ref			Ref		.661
>65	1.001	(0.667–1.502)	.997	1.105	(0.707–1.728)	
Gender						
Male	Ref		.305	Ref		.069
Female	0.795	(0.513–1.232)		0.630	(0.384–1.036)	
Grade						
1	Ref		.052	Ref		.040
2	1.360	(0.653–2.831)		1.476	(0.685–3.183)	
3	2.578	(1.081–6.151)		2.353	(0.960–5.768)	
4	2.670	(0.873–8.169)		0.380	(1.312–27.065)	
PNI						
Negative	Ref		<.001	Ref		.001
Positive	3.378	(1.927–5.921)		3.416	(1.693–6.895)	
LVI						
Negative	Ref		.122	Ref		.849
Positive	1.547	(0.89–2.689)		1.065	(0.555–2.044)	
CRM						
Negative	Ref		.060	Ref		.078
Close / Positive	0.970	(1.365–6.462)				
yp Stage						
0	Ref		.239	Ref		.216
I	0.857	(0.406–1.810)		0.766	(0.358–1.640)	
II	1.423	(0.680–2.977)		1.317	(0.625–2.774)	
III	1.375	(0.685–2.76)		1.265	(0.626–2.556)	
TRG						
0–1	Ref		.574	Ref		.392
2–3	0.942	(0.547–1.623)		0.968	(0.543–1.724)	
4	0.664	(0.293–1.502)		0.279	(0.043–1.816)	

CI = confidence interval, CRM = circumferential resection margin, HR = hazard ratio, LVI = lymphovascular invasion, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PLR = platelet to lymphocyte ratio, PNI = perineural invasion, TRG = tumor regression grade.

* Adjusted for age, gender, grade, PNI, LVI, CRM, yp stage, and TRG.

Table 4

Stratified analyses of NLR and PLR for 5-yr disease free survival and overall survival by post-neoadjuvant pathological (yp) stage.

	5- yr DFS			5-yr OS		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
NLR						
yp stage 0–I						
≤3.5	Ref			Ref		
>3.5	1.533	(0.479–4.900)	.472	1.318	(0.687–2.530)	.406
yp stage II–III						
≤3.5	Ref			Ref		
>3.5	2.334	(1.158–4.725)	.018	2.226	(1.165–4.251)	.015
PLR						
yp stage 0–I						
≤188	Ref			Ref		
>188	2.358	(0.825–6.743)	.110	1.090	(0.600–1.980)	.778
yp stage II–III						
≤188	Ref			Ref		
>188	2.012	(1.049–3.861)	.036	1.552	(0.843–2.859)	.158

DFS = disease free survival, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PLR = platelet to lymphocyte ratio.

independently predicted poor survival (HR = 2.08,95% CI:1.64–2.64). Guo et al[27] conducted pooled analysis of 33 studies containing 15,404 CRC patients; results indicated that elevated PLR was associated with poorer OS (HR = 1.57, 95% CI: 1.41–1.75) and DFS (HR = 1.58, 95% CI: 1.31–1.92). Finally, Gu et al[25] performed a meta-analysis of 13 studies with 8601 CRC patients, again finding that increased PLR predicted poor OS (HR = 1.81, 95% CI: 1.42–2.31) and DFS (HR = 1.84, 95% CI: 1.22–2.76). Therefore, high NLR and high PLR have been proven to forecast poor outcomes in locally advanced and metastatic CRC.

Rectal cancer patients with high NLR but not PLR had significant better DFS and OS in those who underwent neoadjuvant CCRT as a previous study performed by Kim et al[28]. However, Dudani et al[29] concluded that neither NLR nor PLR were found to be independently prognostic for DFS and OS in patients with locally advanced rectal cancer undergoing neoadjuvant CCRT. Consistent with other colorectal studies,[24–27,30] we found that high NLR and PLR were associated with poor DFS. However, NLR was superior to PLR in predicting lower OS in our study. In our stratification analysis, patients with yp stage II to II with high pre-CCRT NLR had significantly poorer DFS and OS; those with yp stage II to II with high pre-CCRT PLR had poorer DFS (HR = 2.012, 95% CI:1.049–3.861, $P = .036$). However, for yp stage 0 to I, NLR and PLR did not affect outcomes. Unlike the numerous published meta-analyses,[24,26] whose heterogenic populations had wide tumor stages, different treatment methods and included those with colon and rectal cancer, our study population was concentrated on rectal cancer patients treated with neoadjuvant CCRT followed by TME, which makes the results more specific and convincing. In addition, previous studies have advocated discrepancy suggestions for the role of adjuvant chemotherapy for patients with rectal cancer after neoadjuvant CCRT followed by Surgery. Anne et al[31] concluded adjuvant chemotherapy did not improve neither OS nor DFS in a meta-analysis. However, Zhifei et al[32] addressed a survival benefit in the use of adjuvant chemotherapy in a retrospective study. The challenge of heterogenic survival behind adjuvant chemotherapy after preoperative CCRT for rectal cancer is still existence. Therefore, knowing pretreatment NLR and PLR in rectal cancer patients receiving neoadjuvant CCRT can help physicians refine additional adjuvant therapeutic decisions.

In previous studies, modifying patients' systemic inflammation response was addressed. Whether altering the pre-CCRT NLR status can influence treatment outcome still need to be unveiled. Some studies have advocated preoperative administration of corticosteroids in patients undergoing operation for cancer can reduce postoperative morbidity.[33,34] Non-steroidal anti-inflammatory drugs (NSAIDS) were also addressed to have effect for against CRC progression.[35] However, we still need further clinical trials to discover whether altering the pre-CCRT NLR status via giving corticosteroids or NSAID can improve survival outcome of rectal cancer patients receiving neoadjuvant CCRT.

This study has some limitations. First, it has the potential for selection bias inherent to retrospective analyses. Second, potential confounding factors such as comorbidities and nutritional status could not be acquired for analysis. However, all recruited patients were within performance status 0 to 1, a fact that may eliminate the effect of these unmeasured factors. Third, all patients in this study were enrolled from an Asian population; therefore, our results should be extrapolated carefully to non-Asian populations. Considering these limitations, a well-designed prospective study is still required to verify this result and apply it to clinical practice.

5. Conclusions

Elevated pre CCRT NLR and PLR are independent prognostic factors for poor outcome in rectal cancer patients. Therefore, pre-CCRT NLR and PLR may be considered as potential biomarkers that need to be further validated by prospective studies, guiding the clinical decision-making process in increasing the intensity of treatment and care for those high-risk patients.

Acknowledgments

The authors express their sincere thanks to the staff of the Cancer Center of the Chi Mei Medical Center for data collection and Gregory Gliemi, Ph.D., for assistance of statistical analyses of the data.

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References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] Wasserberg N. Interval to surgery after neoadjuvant treatment for colorectal cancer. World J Gastroenterol 2014;20:4256–62.
[3] Guillem JG, Chessin DB, Cohen AM, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005;241:829–36. discussion 836-828.
[4] Pease NA, Wise-Draper T, Privette Vinnedge L. Dissecting the potential interplay of DEK functions in inflammation and cancer. J Oncol 2015;2015:106517–106517.
[5] Morrison L, Laukkanen JA, Ronkainen K, et al. Inflammatory biomarker score and cancer: a population-based prospective cohort study. BMC Cancer 2016;16:80.
[6] Klevorn LE, Teague RM. Adapting cancer immunotherapy models for the real world. Trends Immunol 2016;37:354–63.
[7] Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 2013;109:416–21.
[8] Shibutani M, Maeda K, Nagahara H, et al. A high preoperative neutrophil-to-lymphocyte ratio is associated with poor survival in patients with colorectal cancer. Anticancer Res 2013;33:3291–4.
[9] Jung MR, Park YK, Jeong O, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. J Surg Oncol 2011;104:504–10.

[10] Unal D, Eroglu C, Kurtul N, et al. Are neutrophil/lymphocyte and platelet/lymphocyte rates in patients with non-small cell lung cancer associated with treatment response and prognosis? Asian Pac J Cancer Prev 2013;14:5237–42.
[11] Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, et al. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol 2012;23:265–73.
[12] Kim IY, You SH, Kim YW. Neutrophil-lymphocyte ratio predicts pathologic tumor response and survival after preoperative chemo-radiation for rectal cancer. BMC Surg 2014;14:94.
[13] Shen L, Zhang H, Liang L, et al. Baseline neutrophil-lymphocyte ratio (>/=2.8) as a prognostic factor for patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Radiat Oncol 2014;9:295.
[14] Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997;12:19–23.
[15] Nora I, Shridhar R, Huston J, et al. The accuracy of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as a marker for gastrointestinal malignancies. J Gastrointest Oncol 2018;9:972–8.
[16] Bambury RM, Teo MY, Power DG, et al. The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. J Neurooncol 2013;114:149–54.
[17] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
[18] Zhang J, Qiao X, Shi H, et al. Circulating tumor-associated neutrophils (cTAN) contribute to circulating tumor cell survival by suppressing peripheral leukocyte activation. Tumour Biol 2016;37:5397–404.
[19] Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res 2009;69:5383–91.
[20] Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420: 860–7.
[21] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436–44.
[22] Majeti BK, Lee JH, Simmons BH, et al. VEGF is an important mediator of tumor angiogenesis in malignant lesions in a genetically engineered mouse model of lung adenocarcinoma. BMC Cancer 2013;13:213.
[23] Tesfamariam B. Involvement of platelets in tumor cell metastasis. Pharmacol Ther 2016;157:112–9.
[24] Tang H, Li B, Zhang A, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in colorectal liver metastasis: a systematic review and meta-analysis. PLoS One 2016;11:e0159447.
[25] Gu X, Gao XS, Qin S, et al. Elevated platelet to lymphocyte ratio is associated with poor survival outcomes in patients with colorectal cancer. PLoS One 2016;11:e0163523.
[26] Malietzis G, Giacometti M, Kennedy RH, et al. The emerging role of neutrophil to lymphocyte ratio in determining colorectal cancer treatment outcomes: a systematic review and meta-analysis. Ann Surg Oncol 2014;21:3938–46.
[27] Guo Y-H, Sun H-F, Zhang Y-B, et al. The clinical use of the platelet/lymphocyte ratio and lymphocyte/monocyte ratio as prognostic predictors in colorectal cancer: a meta-analysis. Oncotarget 2017;8:20011–24.
[28] Kim TG, Park W, Kim H, et al. Baseline neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in rectal cancer patients following neoadjuvant chemoradiotherapy. Tumori 2019;105:434–40.
[29] Dudani S, Marginean H, Tang PA, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictive and prognostic markers in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation. BMC Cancer 2019;19:664.
[30] Chen N, Li W, Huang K, et al. Increased platelet-lymphocyte ratio closely relates to inferior clinical features and worse long-term survival in both resected and metastatic colorectal cancer: an updated systematic review and meta-analysis of 24 studies. Oncotarget 2017;8:32356–69.
[31] Breugom AJ, Swets M, Bosset JF, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:200–7.
[32] Sun Z, Gilmore B, Adam MA, et al. Adjuvant chemotherapy after preoperative chemoradiation improves survival in patients with locally advanced rectal cancer. Dis Colon Rectum 2017;60:1050–6.
[33] Schmidt SC, Hamann S, Langrehr JM, et al. Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study. J Hepatobiliary Pancreat Surg 2007;14:484–92.
[34] Ramanathan ML, Roxburgh CS, Guthrie GJ, et al. Is perioperative systemic inflammation the result of insufficient cortisol production in patients with colorectal cancer? Ann Surg Oncol 2013;20:2172–9.
[35] Din FV, Theodoratou E, Farrington SM, et al. Effect of aspirin and NSAIDs on risk and survival from colorectal cancer. Gut 2010;59:1670–9.