Journal of
Cancer Science & Therapy

Zaghloul and Abbas, J Cancer Sci Ther 2017, 9:5
DOI: 10.4172/1948-5956.1000458

Research Article OMICS International

The Pre-treatment Systemic Inflammatory Response Biomarkers are Important Determinant of Prognosis for Patients Undergoing Neoadjuvant Therapy for Rectal Cancer

Hala Zaghloul[1] and Ahmed Abbas[2*]
[1]*Clinical Oncology Department, Faculty of Medicine, Alexandria, University, Egypt*
[2]*Surgery Department, National Cancer Institute, Cairo University, Egypt*

Abstract

Purpose: To evaluate the prognostic potential of inflammatory response biomarkers neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) in predicting the outcome of rectal cancer patients undergoing neoadjuvant chemoradiation prior to surgery.

Methods: Retrospective review of T3/T4, or N+ rectal cancer treated with neoadjuvant chemoradiation 50.4 Gy concurrently with either 5 FU (1 g/m^2/d) or Capecitabine 825 mg/m^2 twice daily. Four additional cycles of 5-FU chemotherapy (500 mg/m^2/d, i.v. bolus) or capecitabine (2500 mg/m^2 days 1-14, repeated day 22), were applied post-operatively. Pre-treatment NLR, dNLR, PLR and LMR calculated from peripheral blood cell were compared with clinicopathological parameters. The prognostic value of baseline NLR, dNLR, PLR and LMR for disease free survival (DFS) and overall survival (OS) were assessed using Log rank and Cox regression.

Results: The final analysis included 80 patients, the receiver operating curve (ROC) calculated cut off values of baseline NLR, dNLR, LMR and PLR in predicting outcome were 3, 2.1, 4.9 and 169 respectively. Elevated NLR, dNLR, PLR, LMR, age of patients (≥50 years), depth of invasion ≥T3, lymph node N1-N2, stage III, grade 3 tumors, and partial response to preoperative chemoradiation were significantly associated with decreased OS, and DFS. Multivariate analysis revealed that elevated NLR and dNLR were independent Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation factors for worse OS and DFS hazard ratio (HR) 2.34 (95% CI=3.41-7.24), 4.53 (95% CI, 2.61-8.32) and DSF with (HR) 1.84 (95% CI=2.27-5.36), 4.23 (95% CI=3.49-9.52) respectively.

Conclusion: The baseline NLR, dNLR, LMR and PLR showed a significant association with different clinicopathological prognostic factors in rectal cancer patients receiving preoperative chemoradiation. Additionally, NLR, dNLR may be considered as potential independent prognostic indicators of clinical outcomes.

Keywords: Pre-treatment; Systemic inflammatory response; Biomarkers; Prognostic potential in Rectal Cancer; Chemoradiation

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death in the world [1]. Rectal cancers comprise about one third of surgical resections for colorectal cancer. [2] The standard of care for patients with margin-threatening rectal cancer is preoperative neoadjuvant radiotherapy with or without chemotherapy. This approach significantly increases disease-free survival (DFS) and sphincter preservation rates and improves circumferential resection margins and reduces local recurrence rates [3-6]. The classical TNM staging system which focuses on tumor, nodes, distal metastasis has been commonly considered as "gold standard" for guiding therapy and estimating the outcomes in patients with CRC [7]. However, these systems are limited for predicting the prognosis precisely and guiding the clinical practice appropriately, because many patients with the same stage turned out to have significantly heterogeneous prognosis [8,9]. Therefore, there is a need to identify biomarkers of response because treatment is associated with significant morbidity, as not all patients respond to neoadjuvant chemoradiation (nCRT). Recently, the systemic inflammation biomarkers were found to provide insight into prognosis of solid tumors [10,11]. Several indicators derived from the peripheral blood such as the neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) have been widely investigated as useful prognostic indicators in various kinds of cancers including gastric cancer, colorectal cancer, hepatocellular carcinoma, non-small cell lung cancer, breast cancer and pancreatic cancer. [12,13] An elevated NLR has been found to be an indicator of poor prognosis in patients with CRC [14]. On the other hand, PLR role as prognostic indicator was found to be inconsistent as it was associated with decreased survival in some studies [15,16], whereas others did not demonstrate the relationship between prognosis and PLR [17,18]. However, only one or two inflammatory biomarkers have been evaluated for the prognosis of patients with rectal cancer according to previous reports [19-21]. Moreover, the optimal cut-off values of the biomarkers from these studies were still inconsistent. Consequently, further study on the prognostic values of these biomarkers in patients with rectal cancer is necessary. This study aimed to evaluate the prognostic potential of

***Corresponding author:** Dr. Hala Ahmed Zaghloul Isamil El Lathy, Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Alexandria University, Egypt, Tel: 00201223926059; Fax: 002034290746; E-mail: h_zagloul@yahoo.com

Received April 29, 2017; **Accepted** May 22, 2017; **Published** May 26, 2017

Citation: Zaghloul H, Abbas A (2017) The Pre-treatment Systemic Inflammatory Response Biomarkers are Important Determinant of Prognosis for Patients Undergoing Neoadjuvant Therapy for Rectal Cancer. J Cancer Sci Ther 9: 451-459. doi: 10.4172/1948-5956.1000458

NLR, dNLR, PLR and LMR biomarkers in predicting the outcome of rectal cancer patients undergoing neoadjuvant chemoradiation prior to surgical resection.

Material and Methods

Retrospective review of rectal cancer patients treated at or referred to Clinical Oncology department Alexandria University and Surgical Oncology department and National Cancer Institute Cairo University between January 2012 and February 2016 after obtaining institutional board approval (IRB) approval. All patients signed informed consent. Medical records were reviewed to select rectal cancer who received neoadjuvant chemoradiation prior to surgical resection to determine known prognostic variables including: age, histology, grade, surgical stage, response to neoadjuvant chemoradiation, in addition to the tested pre-treatment prognostic biomarkers neutrophil count to lymphocyte count (NLR), derived neutrophil to lymphocyte ratio (dNLR) was constructed as follows: dNLR=neutrophil count to (white cell count-neutrophil count), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) were calculated from peripheral blood cell count which were calculated from peripheral blood count.

Inclusion criteria

1-Non-metastatic, localized, histologically proven clinically staged T3/T4, or N+ rectal cancer (included lesions up to 16 cm from verge).

2- Neoadjuvant chemoradiation consisted of 50.4 Gy in 1.8 Gy fractions given to the tumor and pelvic lymph nodes given concurrently with either 5 FU (1 g/m2/d) during first and fifth weeks of radiation (as 120 hr infusion), or 5FU (400 mg/m^2/d) intravenous (iv) bolus and leucovorin 20 mg/m^2 iv bolus for 4 days during the first and fifth weeks of radiation. Alternatively, Capecitabine 825 mg/m^2 twice daily five days per week concurrent with radiation. Total mesorectal excision (TME) surgery was performed 4-6 weeks after completion of neoadjuvant CRT. Four additional cycles of 5-FU chemotherapy (500 mg/m^2/d, i.v. bolus) or capecitabine (2500 mg/m^2 days 1-14, repeated day 22), were applied post-operatively.

Assessment of response to nCRT

Radiologic response to therapy was assessed using RECIST criteria 1.1 and was defined as both primary tumor and lymph nodes downstaging based on comparing pre- and post-neoadjuvant treatment MRI [22]. Total mesorectal excision (TME) was performed in all patients, however extent of surgery whether low anterior or abdominoperineal resection was based on the initial tumor location. Surgery were performed 4-6 weeks after completion of neoadjuvant CRT. Adjuvant CTx started 4 weeks after surgery.

3-Only patients with R0 resection were included. R0 resection was defined as removal of all gross tumor and histopathologic examination of proximal, distal, and circumferential margins that revealed the absence of malignant cells more than 2 mm from the edge.

Exclusion criteria

1. Patients who develop evidence of distant metastasis during induction phase were not eligible for surgical resection.

2. Patients with R1 resection (microscopic residual) or R2 resection (gross residual), or M1 carcinoma.

3. After operation, each patient was followed up regularly until December 2016 or until death (every 3 months for the first 2 years and then every 6 months up to 5th year). Physical examination, endoscopy, laboratory tests and imaging were conducted at every visit. The follow-up periods varied from 3 months to 50 months, with a median of 25 months. Overall survival (OS) was calculated from diagnosis to death. For drop-out patients, the date of the last follow-up was applied. Disease-free survival (DFS) was calculated from surgery to disease relapse or until the date of last follow-up.

Statistical Consideration

The impact of different clinical parameters on Baseline response inflammatory biomarkers (NLR, dNLR, LMR and PLR) were evaluated by Mann-Whitney U test (between 2 groups) or Kruskal-Wallis test (≥3 groups). Receiver operator characteristic (ROC) curves were used to identify potential Baseline response inflammatory biomarkers cut-offs values in rectal cancer patients treated with neoadjuvant concurrent chemoradiation prior to surgical resection. An area under the curve of 1.0 would indicate a perfect test, whereas 0.5 would represent a non-informative test. Kaplan-Meier method was accessed for survival analysis.

Prognostic variables identified by univariate analysis, with $P<0.1$, were analyzed in the multivariate Cox model. All reported P-values were two-sided. Statistical significance levels were set at $P<0.05$. Disease free survival (DFS) and overall survival (OS) were calculated using the Kaplan Meier analysis. Log-rank test and Cox regression analysis were performed to correlate the various clinical and pathological parameters to treatment outcomes. All analyses were performed using SPSS 16.0 package program, (SPSS, Chicago, IL).

Results

This study included 90 rectal cancer patients who received neoadjuvant chemoradiation. The final analysis included 80 patient who had total mesorectal excision with R0 resection after neoadjuvant chemoradiation with 54 (67.5%) male and 26 (32.5%) female, patients aged from 38 to 69 (the median age was 52 years). With regards to histological type, the number of moderately, poorly differentiated, mucinous and signet ring cell carcinoma were 56 (70%), 5 (6.3%), 7 (8.8%) and 6 (7.5%) respectively. Based on the seventh edition of the TNM-UICC/AJCC classification, the number of baseline clinical stage IIA, IIB, III (Any T N1, N2) were 8 (10%), 10 (12.5%) and 62 (77.5%) respectively. Additionally, the median values of baseline NLR, dNLR, LMR and PLR were 3.8, 3, 4.2 and 156 respectively. All patients baseline characteristics are presented in Table 1.

The optimal thresholds for NLR, dNLR, PLR and LMR

The receiver operating characteristic (ROC) curve, used DFS as the end-point for NLR, dNLR, PLR and LMR (Figure 1). The receiver operating curve (ROC) demonstrated a baseline NLR of 3 cut off value (area under the curve: 0.778) for predicting DFS with a sensitivity 78.7% and septicity of 85.3%. Additionally, the dNLR cut off 2.1 (area under the curve: 0.740) yielded a sensitivity of 77.3% and specificity of 84.3% in predicting the DFS. Moreover, the ROC curve illustrated the ability of baseline LMR and PLR to predict DFS (area under the curve were 0.612 and 0.545 and the best cut-off value were 4.9, 169 respectively). The base line LMR 4.9 cutoff value yielded a sensitivity of 68.7% and specificity of 76.5% in predicting DFS respectively. Moreover, PLR 169 cut off value resulted in the lowest sensitivity of 60.1% and septicity 68.3% in predicting DFS. Patients were subsequently divided into two groups according to the optimal cut-off levels, with the high group ≥ the optimal cut-off levels and the low group that < the optimal cut-off levels. Our results revealed that NLR, dNLR, PLR and LMR were significantly associated with tumor stage, depth of invasion, lymph

Characteristic	No. of Patients	%
Age, years		
Median	52	
<50	36	45%
≥50	44	55%
Sex		
Male	54	67.5%
Female	26	32.5%
Zubrod performance scale		
0	36	45%
1	38	47.5%
2	6	7.5%
Histopathological type		
Well differentiated	6	7.5 %
Moderately differentiated	56	70%
Poorly differentiated	5	6.3%
Mucinous	7	8.7%
Signet Ring	6	7.5%
T stage		
T1	12	11.5%
T2	18	22.5%
T3	44	55%
T4a,b	6	7.5%
N stage		
N0	18	22.5%
N1	48	60%
N2	14	17.5%
Stage group		
IIA	8	10%
IIB, C	10	12.5%
III (Any T N1, N2)	62	77.5%
Vascular invasion		
No vascular invasion	48	60%
Vascular invasion	32	40%
Inflammatory response biomarkers		
NLR		
Median	3.8	
< 3	54	67.5%
≥ 3	26	32.5%
dNLR		
Median	3	
< 2.1	48	60%
≥ 2.1	32	40%
LMR		
Median	4.2	
< 4.9	49	61.2%
≥ 4.9	31	38.8%
LMR		
Median	156	
< 169	47	58.7%
≥ 169	33	41.3%
Surgical procedure		
Anterior resection	56	70%
Abdominoperineal resection	24	30%
Radiological response		
Complete response unknown	10	12.5%
Partial response ≥30%	33	41.3%
Stable disease	22	27.5%
Progressive disease	15	18.7%

Table 1: Patient characteristics at baseline (N=80).

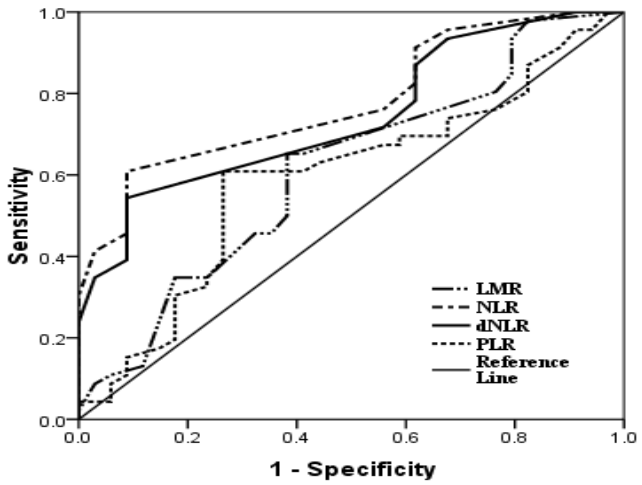

Figure 1: The receiver operator curve (ROC) of baseline NLR, dNLR, LMR, PLR in rectal cancer patients.

node, histological types and tumor grade respectively. On the contrary, NLR, dNLR, PLR and LMR were not associated with the age or sex of patients. Those patients with tumor stage III (Any T N1, N2) depth of invasion T3-T4, and lymph node N1-N2 had a higher NLR, dNLR, LMR and PLR than those with tumor stage II, depth of invasion T1-T2, and lymph node N0 (Table 2).

Surgical procedure and postoperative pathology

Ninety patients were assessed for surgery after neoadjuvant chemoradiation. Eighty patients (88%) had an R0 resection, whereas 6 patients (6%) had R1 resection. Surgery was not done in the remaining four patients due to distant metastasis. Our study scrutinized on the 80 patients who had R0 resection and excluded the remaining 10 patients who had either R1 resection or declined surgical due to disease progression. Moreover, a pathological complete response (path CR) was noted in both primary tumor sites and associated regional lymph nodes in 10 patients (12.5%) while a partial pathological response (path PR) was encountered in the remaining 64 patients (80%). Thus, the overall pathologic response rate was achieved in 74 patients (92.5%) while the remaining 6 patients (7.5%) had stable or progressive disease after concurrent chemoradiation. In the 80 patients who had a TME, the primary carcinoma was T3 in 15patients (18.7%), T2 in 12 patients (15%), T1 in 27 patients (33.8%), and T0 in 20 patients (25%). Twenty eight (35%) of the 80 patients who underwent TME had N0 cancer, 40 patients (50%) had N1 cancer, and 12 patients (15%) had N2 cancer and 10 patients had combined T0 N0 (path PCR) (Table 3). The median number of nodes examined in the 80 TME specimens was 16 (range, 6 to 22 nodes). The median number of nodes with carcinoma was 4, and the median number of cancer-free nodes was 12.

Clinical factors associated with path CR

Many clinical factors were tested for their impact on achieving pathological complete response such as sex, cancer location, histopathological type, baseline T-stage, and baseline N stage. The histopathological type (P=0.03), the baseline T-stage (P=0.002), N stage (P=0.001), in addition to inflammatory response biomarkers NLR (P=0.001), d NLR (P=0.002), LMR (P=0.001) and PLR (P=0.003) were significantly associated with path CR (Table 4) and any pathologic response.

Characteristic	No. of Patients	%	Baseline NLR		Baseline dNLR		Baseline LMR		Baseline PLR	
			Median	*P* value	Median	*P* value	Median	*P* value	Median	*P* value
Age, years										
< 50	36	45%	2.7	0.646	1.9	0.478	3.6	0.347	154	0.673
≥50	44	55%	3		1.8		3.9		159	
Sex										
Male	54	67.5%	2.6	0.684	1.9	0. 473	3.6	0.521	142	0.684
Female	26	32.5%	2.9		2.1		3.9		145	
Histopathological type										
Well differentiated	6	7.5%	1.8	**0.0312***	1.9	0.**0232***	2.5	**0.0121***	123	**0.0136***
Moderately differentiated	56	70%	2.3		2.1		3.6		143	
Poorly differentiated	5	6.3%	4.5		4.9		5.4		169	
Mucinous	7	8.5%	3.6		3.7		4.9		151	
Signet Ring	6	7.5%	3.9		3.8		5.2		165	
T stage										
T1	12	11.5%	1.9	**0.0216***	1.8	**0.0315***	3.2	**0.0316***	123	**0.0126***
T2	18	22.5%	2.6		2.3		3.6		147	
T3	44	55%	4.5		4.2		5.6		149	
T4 a, b	6	7.5%	4.9		5				168	
N stage										
N0	18	22.5%	1.8	**0.0134***	1.7	**0.0146***	2.9	**0.0124***	122	**0.0122***
N1	48	60%	2.9		2.4		4.1		148	
N2	14	17.5%	4.9		4.8		5.9		169	
Stage group										
IIA	8	10%	2.5	**0.0145***	2.2	**0.0121***	3.2	**0.014***	134	**0.001***
IIB, C	10	12.5%	4.7		2.9		4.9		148	
III (Any TN1, N2)	62	77.5%	5.9		5.5		5.9		170	
Vascular invasion										
No vascular invasion	48	60%	2.3	**0.0132***	2.1	**0.003***	2.8	**0.0114***	121	**0.002***
Vascular invasion	32	40%	5.6		5.1		4.9		165	

Table 2: Association between inflammatory biomarkers and different clinicopathological parameters.

	Baseline		After induction chemoradiation		Wilcoxon Signed Rank Test Asymp. sig (2 tailed)
	No of pts %		No of pts %		
T stage					
T0	0		20	25%	**0.001***
T1	12	11.5%	27	33.8%	
T2	18	22.5%	12	15%	
T3	44	55%	15	18.7%	
T4 a, b	6	7.5%	6	7.5%	
N stage					
N0	18	22.5%	28	35%	**0.024***
N1	48	60%	40	50%	
N2	14	17.5%	12	15%	

Table 3: Patient response to chemoradiotherapy (N=80).

The association between baseline characteristics and clinical prognosis

The median follow-up period was 26 months. During the follow-up period, 26 (32.5%) patients were detected as local recurrence or distant metastasis. Among them, 22 (27.5%) patients were dead from cancer-related disease. The median of DFS and OS was 24 months and 28 months, respectively. Moreover, the 3-year overall survival and disease-free survival were 72.5% and 67.5% respectively (Figures 2 and 3). To evaluate the association of baseline characteristics with clinical prognosis, Kaplan-Meier survival analysis and log-rank tests were performed. Our results indicated that age of patients (≥50 years), depth of invasion >T3, lymph node N1-N2, stage III, grade 3 tumors, and partial response to preoperative chemoradiation (Figures 4 and 5), NLR (≥3), (Figures 6 and 7), dNLR (≥2.1) (Figures 8 and 9), PLR (≥169), LMR (≥ 4.9) were significantly associated with decreased OS, and DFS (Table 5). Cox regression multivariate for overall survival revealed that higher baseline NLR, dNLR along with advanced TNM stage at diagnosis and partial response following neoadjuvant chemoradiation were independently correlated with OS, with hazard ratio 2.34 (95% confidence interval [CI], 3.41-7.24), 4.53 (95% CI, 2.61-8.32), 4.21 (95% CI, 2.24-9.73) and 4.36 (95% CI, 2.27-9.34) respectively. Similarly, multivariate analysis for disease free survival demonstrated that higher baseline NLR, dNLR along with advanced TNM stage at diagnosis, partial response following neoadjuvant chemoradiation were independently correlated with poor DFS, with hazard ratio 1.84 (95% confidence interval [CI], 2.27-5.36), 2.63 (95% CI, 2.61-8.12), 6.21 (95% CI, 1.28-14.23), 7.35 (95% CI, 3.57-11.54) and 4.23 (95% CI, 3.49-9.52), respectively.

Discussion

Over the past decades, more understanding of the links between inflammatory microenvironment and cancer has emerged and contributed significantly to the prognosis of many tumors. A series of inflammatory cells and innate immune system signaling molecules are involved in tumor progression [23], such as neutrophil, lymphocyte, platelet and monocyte. Thus, NLR, d-NLR, PLR and LMR that represent systematic inflammatory response are potential prognostic factors for CRC. [24] Consequently, our study aimed to evaluate the prognostic

Characteristic	Patients	Complete pathologic response. Total=10 Pts		*P Value*	Partial pathologic response Total=64 pts		*P value*
		No	%CR		No	%PR	
Age, years							
< 50	36	5	50%	0.74	30	46.8%	0.91
≥50	44	5	50%		34	53.2%	
Sex							
Male	54	5	50%	0.82	43	67.2%	0.88
Female	26	5	50%%		21	32.8%	
Histopathological type							
Well differentiated	6	4	40%		2	3.1%	
Moderately differentitred	56	6	60%	**0.03***	50	78.1%	**0.02***
Poorly differentiated	5	0	0%		4	6.3%	
Mucinous	7	0	0%		6	9.3%	
Signet Ring	6	0	0%		2	3.1%	
T stage							
T1	12	2	20%		10	15.6%	
T2	18	2	20%	**0.002***	16	25%	**0.001***
T3	44	6	60%		38	59.4%	
T4 a, b	6	0	0%				
N stage							
N0	18	8	80%	**0.001** *	10	15.6%	**0.003***
N1	48	2	20%		46	71.9%	
N2	14	0	0%		8	12.5%	
Stage group							
IIA	8	6	60%		2	3.1%	
IIB, C	10	0	0%	**0.01***	10	15.6%	**0.03***
III (Any T N1, N2)	62	4	40%		52	81.3%	
Vascular invasion							
No vascular invasion	48	8	80%%	**0.001** *	46	71.9%	**0.002***
Vascular invasion	32	2	2%		18	28.1%	
Inflammatory response biomarkers							
NLR							
Median	3.8						
< 3	54	9	90%	**0.001***	45	70.3%	**0.003***
≥ 3	26	1	10%		19	29.6%	
dNLR							
Median	3						
< 2.1	48	8	80%	**0.002***	40	62.5%	
≥ 2.1	32	2	20%		24	37.5%	
LMR							
Median	4.2						
< 4.9	49	7	70%	**0.001***	42	65.6%	**0.04***
≥ 4.9	31	3	30%		22	34.4%	
PLR							
Median	159						
< 169	47	6	60%	**0.003***	41	64%	**0.001***
≥ 169	33	4	40%		23	36%	

Table 4: Association between pathological response and different clinicopathological parameters.

potential of NLR, dNLR, PLR and LMR biomarkers in predicting the outcome of rectal cancer patients undergoing neoadjuvant chemoradiation prior to surgical resection. The (ROC) demonstrated the ability of a baseline NLR, dNLR, LMR and PLR to predict DFS in this group of rectal cancer patients with area under the curve (AUC) of 0.778, 0.740, 0.612 and 0.545 respectively. Similarly, Ying et al reported that preoperative NLR, d-NLR, PLR could be considered as potential biomarkers for colorectal cancer patients with ROC area under the curve (AUC) of 0.764, 0.672, 0.727 respectively. However, they could not use LMR for subsequent analysis for its low AUC of 0.234 [25]. A possible reason for such difference in the prognostic potential of baseline LMR between our study and Ying et al might be related to the studied population as we focused only rectal cancer patients while they included both colon and rectal cancer patients. Moreover, our results demonstrated that patients with tumor stage III (Any T N1, N2) depth of invasion T3-T4, and lymph node N1-N2 had a higher NLR, dNLR, LMR and PLR than those with tumor stage II, depth of invasion T1-T2, and lymph node N0. Ying et al reported comparable association between advanced stage disease, T3-T4 depth of invasion, advanced nodal disease and elevated baseline biomarkers NLR, dNLR, LMR and PLR [25].

To the best of our knowledge, this retrospective study represents the first series that succeeded to find out cut off values of baseline

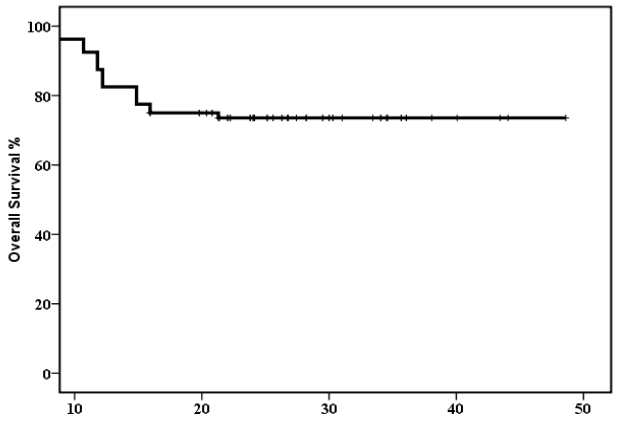

Figure 2: Overall Survival in months in rectal cancer patients treated with neoadjuvant chemoradiation.

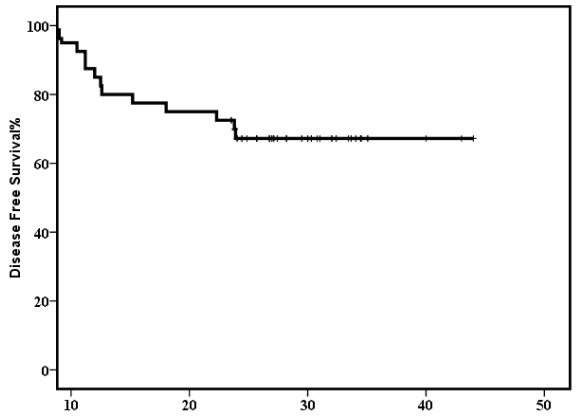

Figure 3: Disease free Survival in months in rectal cancer patients treated with neoadjuvant chemoradiation.

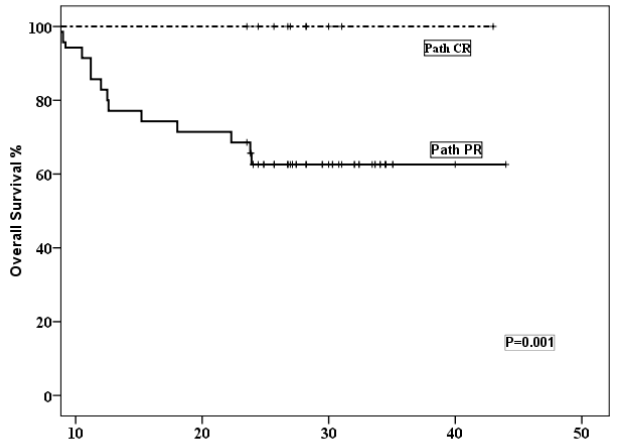

Figure 4: Overall survival by pathological response in months.

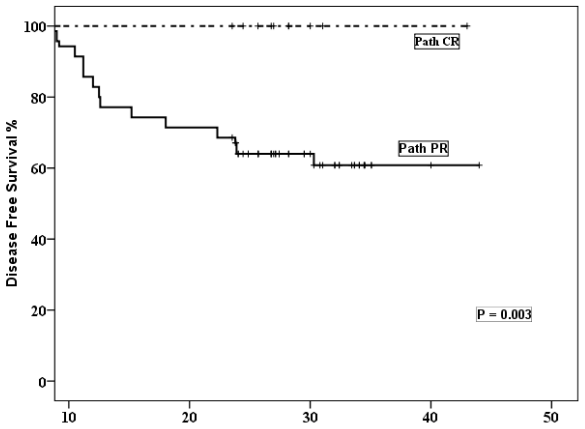

Figure 5: Disease free survival by pathological response in months.

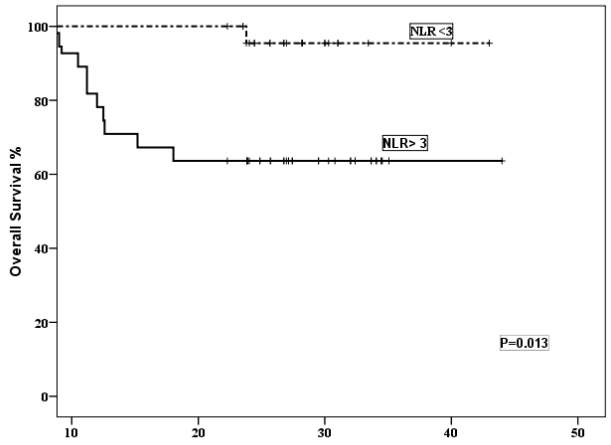

Figure 6: Overall survival by NLR cutoff level in months.

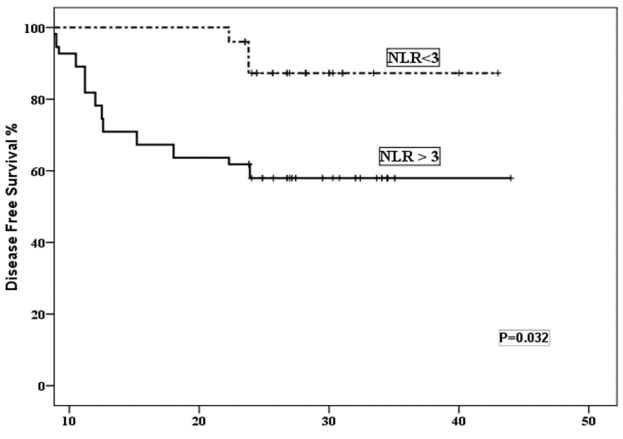

Figure 7: Disease free survival by NLR cutoff level in months.

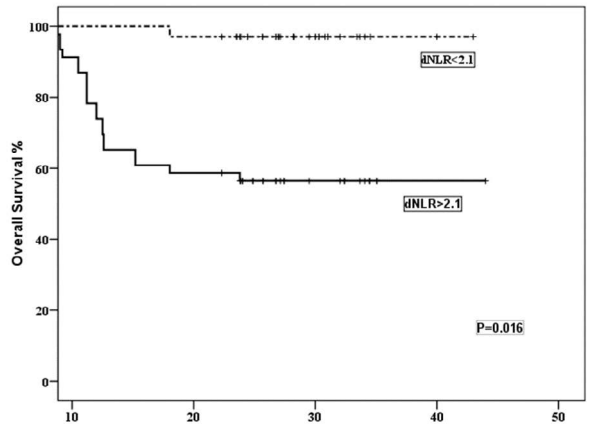

Figure 8: Overall survival by dNLR cutoff level in months.

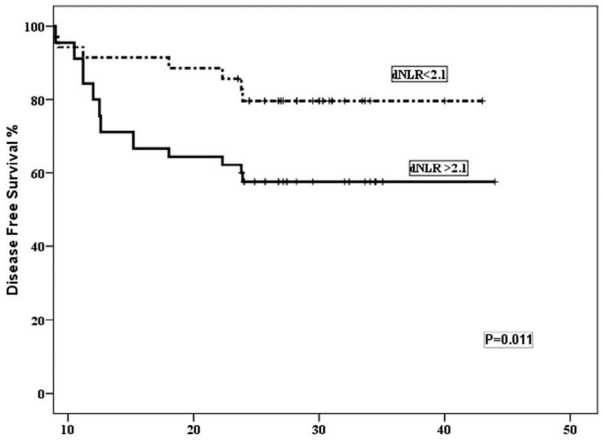

Figure 9: Disease free survival by dNLR cutoff level in months.

biomarkers NLR, dNLR, LMR and PLR for rectal cancer patient receiving neoadjuvant chemoradiation prior to surgical resection. More importantly, our study demonstrated that baseline inflammatory response biomarkers NLR (P=0.001, d NLR (P=0.002), LMR (P=0.001) and PLR(P=0.003) were significantly associated with path CR and any pathologic response.

It is worth mentioning that our results indicated that age of patients (≥50 years), depth of invasion ≥T3, lymph node N1-N2, stage III, grade ≥3 tumors, and partial response to preoperative chemoradiation, NLR (≥3), dNLR (≥2.1), PLR (≥169), LMR (≥ 4.9) were significantly associated with decreased OS, and DFS. However, multiple regression analysis revealed that higher baseline NLR, dNLR along with advanced TNM stage at diagnosis and partial response following neoadjuvant chemoradiation were independently correlated with poor OS and DFS. Correspondingly, Ying et al. reported that in multivariate analysis, elevated NLR, high tumor grade and stage showed a significant association with OS, CSS and DFS [25]. Our findings are consistent with previous studies on the relationship of NLR and prognosis of many other cancers, such as breast cancer, pancreatic cancer, hepatocellular carcinoma [26-28], especially CRC [29,30].

The above results were supported by several mechanisms of inflammatory reaction to tumor. Basically, neutrophils interacted with distinct cell populations and produced a wide number of cytokines and effector molecules, such as circulating vascular endothelial growth factor (VEGF). VEGF stimulated tumor angiogenesis, growth and metastasis [31]. VEGF-A and VEGF-C were observed significantly higher expression in CRC tissue in comparison with normal tissues [29], and reduced expression of VEGF and VEGFR contributes to markedly inhibited CRC tumor neovascularization *in vivo* and *in vitro* [32,33].

Additionally, neutrophil could be triggered by cancer-related inflammatory factors such as interleukin-6, tumor necrosis factor alpha and granulocyte colony-stimulating factor, myeloid growth factors produced by cancer cell [32-37]. On the other hand, human immune response triggered by colorectal cancer mainly relays on lymphocytes, whereas systematic inflammation significantly depressed cellular immunity, resulting in a significantly decrease of CD4/T lymphocytes and an increasing of CD8/suppressor T lymphocytes [38,39]. Thus, cancer-triggered inflammation resulted in elevated NLR. Meanwhile, elevated NLR promoted cancer progression, eventually resulting in an unfavourable prognosis in surgical CRC patients.

The current study has several strengths

First: It is considered to be the first study to confirm the impact of different clinicopathological prognostic indicators including baseline inflammatory response biomarkers (NLR, dNLR, PLR, and LMR) on the outcome of rectal cancer patients treated with preoperative concurrent chemoradiation.

Second: There was homogeneity in the treatment used as all patients received neoadjuvant concurrent chemoradiation prior to surgical resection, which obviated the possible negative impact of different treatment modalities on clinical prognosis.

There are limitations to the current study

Firstly, the study was a retrospective design, with a small population size of 80 patients.

Secondly, the peripheral blood findings were not compared to the findings of peritumoral inflammation in the primary tumor tissue. Consequently, further studies are needed to illuminate the relationship between inflammatory biomarkers and prognosis in patients with rectal cancer treated with preoperative concurrent chemoradiation.

Conclusion

This study demonstrates that the baseline inflammatory response biomarkers NLR, dNLR, PLR and LMR showed a statistically significant association with different clinicopathological prognostic factors. In addition, NLR, dNLR may be considered as a potential independent prognostic indicator of clinical outcomes in rectal cancer patients receiving neoadjuvant chemoradiation. Ultimately prospective studies will be needed to further validate the prognostic potential of the baseline inflammatory response biomarkers in rectal cancer patients.

Conflict of Interest

All authors confirm that they did not receive any funds nor financial support from the institutes they are affiliated to nor any other companies. Moreover, all authors affirm that they have no conflicts of interest concerning this study.

Characteristic	No. of Patients and %	Overall survival No (%) of patients alive 58		Disease free survival No (%) of patients 52 free of disease	
Age, years			***P* value**		
<50	38 (45%)	26 (44.8%)	**0.01***	22(42.3%)	**0.012***
≥50	44 (55%)	32 (55.2%)		30 (57.7%)	
Sex					
Male	54(67.5%)	28(48.3%)	0.534	27(51.9%)	0.612
Female	26(32.5%)	30 (51.7%)		25(48.1%)	
Histopathological type at diagnosis					
Well differentiated	6 (7.5%)	6 (10.3%)		6 (11.5%)	
Moderately differentiated	56 (70%)	49 (84.5%)		44 (84.6%)	
Poorly differentiated	5 (6.3%)	2 (3.5%)	**0.002***	1(1.9 %)	**0.011***
Mucinous	7(8.7%)	1 (1.7%)		1(1.9%)	
Signet Ring	6(7.5%)	0		0	
T stage at diagnosis					
T1	12(11.5%%)	12(20.6%)		12 (23.1%)	
T2	18 (22.5%)	18(31%)	**0.003***	17 (32.7%)	**0.012***
T3	44(55%)	31 (53.4%)		23 (44.2%)	
T4	6 (7.5%)	1(1.7%)		0	
N stage at diagnosis					
N0	18 (22.5%)	18(31%)		18(34.6%)	
N1	48 (60%)	36(62%)	**0.02***	32 (61.5%)	**0.031***
N2	14 (17.5%)	4(7%)		2 (3.9%)	
Stage group at diagnosis					
IIA	8 (10%)	8(13.8%)		8 (15.4%)	
IIB, C	10 (12.5%)	1 (1.7%)	**0.01***	0	**0.04***
III (Any T N1, N2)	62 (77.5%)	49 (84.5%)		44 (84.6%)	
Pathological response					
Complete response at primary site and LN	10 (12.5%)	10 (17.2%)		10 (19.2%)	
Partial response	64 (80%)	46 (79.3%)	**0. 001***	42 (80.8%)	**0.003***
Stable or progressive disease	6 (7.5%)	2 (3.5%)		0	
Inflammatory response biomarkers at diagnosis					
NLR					
Median	3.8				
< 3	44(55%)	42 (72.4%)	**0.013***	40(77%)	**0.032***
≥ 3	36(45%)	16(27.6%)		12(23%)	
dNLR					
Median	3				
< 2.1	48 (60%)	45 (77.6%)	**0.016***	41 (79%)	**0.011***
≥ 2.1	32 (40%)	13 (22.4%)		11 (21 %)	
LMR					
Median	4.2				
< 4.9	49 (61.2%)	46 (79.3%)	**0. 014***	42 (80.8%)	**0. 021***
≥ 4.9	31 (38.8%)	12 (20.7%)		10 (19.2%)	
PLR					
Median	156				
< 169	47(58.7%)	41(70.7%)	**0.027***	39 (75%)	**0.001***
≥ 169	33 (41.3%)	17 (29.3%)		13 (25%)	

Table 5: Association between different clinicopathological parameters and clinical prognosis.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66: 7-30.
2. Powell AG, Wallace R, McKee RF, Anderson J, Going JJ, et al. (2012) The relationship between tumour site, clinicopathological characteristics, and cancer-specific survival in patients undergoing surgery for colorectal cancer. Colorectal Dis 14: 1493-1499.
3. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, et al. (2009) Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 27: 5124-5130.
4. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, et al. (2004) Pre-operative versus post-operative chemoradiotherapy for rectal cancer. N Engl J Med 351: 1731-1740.
5. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, et al. (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicentre, randomised trial. Lancet 373: 811-820.
6. Quirke P (2003) Training and quality assurance for rectal cancer: 20 years of data is enough. Lancet Oncol 4: 695-702.
7. Hari DM, Leung AM, Lee JH (2013) AJCC cancer staging manual 7th edition criteria for colon cancer: Do the complex modifications improve prognostic assessment? J Am Coll Surg 217: 181-190.

8. Trakarnsanga A, Gonen M, Shia J (2014) Comparison of tumor regression grade systems for locally advanced rectal cancer after multimodality treatment. J Natl Cancer Inst 106: 248.

9. Benson AB3rd, Schrag D, Somerfield MR (2004) American society of clinical oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 22: 3408-3419.

10. Templeton AJ, McNamara MG, Seruga B (2014) Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 106: 124.

11. Sideras K, Kwekkeboom J (2014) Cancer inflammation and inflammatory biomarkers: Can neutrophil, lymphocyte, and platelet counts represent the complexity of the immune system? Transplant Int 27: 28-31.

12. Ong SL, Garcea G, Thomasset SC (2008) Surrogate markers of resectability in patients undergoing exploration of potentially resectable pancreatic adenocarcinoma. J Gastrointest Surg 12: 1068-1073.

13. Chang H, Gao J, Xu BQ (2013) Haemoglobin, neutrophil to lymphocyte ratio and platelet count improve prognosis prediction of the TNM staging system in nasopharyngeal carcinoma: Development and validation in 3,237 patients from a single institution. Clin Oncol (R Coll Radiol) 25: 639-646.

14. Li MX, Liu XM, Zhang XF (2014) Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: A systematic review and meta-analysis. Int J Cancer 134: 2403-2413.

15. Liu H, Du X, Sun P (2013) Preoperative platelet-lymphocyte ratio is an independent prognostic factor for resectable colorectal cancer. Nan Fang Yi Ke Da Xue Xue Bao 33: 70-33.

16. Ozawa T, Ishihara S, Nishikawa T (2015) The preoperative platelet to lymphocyte ratio is a prognostic marker in patients with stage II colorectal cancer. Int J Colorectal Dis 30: 1165-1171.

17. Baranyai Z, Krzystanek M, Josa V (2014) The comparison of thrombocytosis and platelet-lymphocyte ratio as potential prognostic markers in colorectal cancer. Thromb Haemost 111: 483-490.

18. Ying HQ, Deng QW, He BS (2014) The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol (Northwood, London, England) 31: 305.

19. Neofytou K, Smyth EC, Giakoustidis A (2014) Elevated platelet to lymphocyte ratio predicts poor prognosis after hepatectomy for liver only colorectal metastases, and it is superior to neutrophil to lymphocyte ratio as an adverse prognostic factor. Med Oncol (Northwood, London, England) 31: 239.

20. Kwon HC, Kim SH, Oh SY (2012) Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers 17: 216.

21. Son HJ, Park JW, Chang HJ (2013) Preoperative plasma hyper fibrinogenemia is predictive of poor prognosis in patients with non-metastatic colon cancer. Ann Surg Oncol 20: 2908-2913.

22. Eisenhauer EA, Therasse P, Bogaerts J (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) Eur J Cancer 45: 228-247.

23. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420: 860-867.

24. Cedre´s S, Torrejon D, Martı´nez A, Martinez P, Navarro A, et al. (2012) Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. Clin Transl Oncol 14: 864-869.

25. Ying HQ, Deng QW, He BS (2014) The prognostic value of preoperative NLR, d-NLR, PLR and LMR for predicting clinical outcome in surgical colorectal cancer patients. Med Oncol 2014 31: 305.

26. Cedre´s S, Torrejon D, Martı´nez A, Martinez P, Navarro A, et al. (2012) Neutrophil to lymphocyte ratio (NLR) as an indicator of poor prognosis in stage IV non-small cell lung cancer. Clin Transl Oncol 14: 864-869.

27. Stotz M, Gerger A, Eisner F, Szkandera J, Loibner H, et al. (2013) Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. Br J Cancer 109: 416-421.

28. Mano Y, Shirabe K, Yamashita Y, Harimoto N, Tsujita E, et al. (2013) Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: A retrospective analysis. Ann Surg 258: 301-305.

29. Shibutani M, Maeda K, Nagahara H, Noda E, Ohtani H, et al. (2013) Significance of preoperative neutrophil-to-lymphocyte ratio as a predictor of prognosis in patients with stage IV colorectal cancer. Gan To Kagaku Ryoho 40: 1603-1605.

30. Shibutani M, Maeda K, Nagahara H, Noda E, Ohtani H, et al. (2013) A high preoperative neutrophil-to-lymphocyte ratio is associated with poor survival in patients with colorectal cancer. Anticancer Res 33: 3291-3294.

31. Kusumanto YH, Dam WA, Hospers GA, Meijer C, Mulder NH (2003) Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis 6: 283-287.

32. Hanrahan V, Currie MJ, Gunningham SP, Morrin HR (2003) The angiogenic switch for vascular endothelial growth factor (VEGF)-A, VEGF-B, VEGF-C, and VEGFD in the adenoma-carcinoma sequence during colorectal cancer progression. J Pathol 200: 183194.

33. Kim SL, Lee ST, Trang KT, Kim SH, Kim IH, et al. (2014) Parthenolide exerts inhibitory effects on angiogenesis through the down regulation of VEGF/VEGFRs in colorectal cancer. Int J Mol Med 33: 1261-1267.

34. Kuper H, Adami HO, Trichopoulos D (2000) Infections as a major preventable cause of human cancer. J Intern Med 248: 171-183.

35. Blaser MJ, Chyou PH, Nomura A (1995) Age at establishment of Helicobacter pylori infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk. Cancer Res 55: 562-565.

36. Scholl SM, Pallud C, Beuvon F, Hacene K, Stanley ER, et al. (1994) Anti-colony-stimulating factor-1 antibody staining in primary breast adenocarcinomas correlates with marked inflammatory cell infiltrates and prognosis. J Natl Cancer Inst 86: 120-126.

37. Shacter E, Weitzman SA (2002) Chronic inflammation and cancer Oncology 16: 217-226.

38. Rabinowich H, Cohen R, Bruderman I, Steiner Z, Klajman A (1987) Functional analysis of mononuclear cells infiltrating into tumors: Lysis of autologous human tumor cells by cultured infiltrating lymphocytes. Cancer Res 47: 173-177.

39. Menges T, Engel J, Welters I, Wagner RM, Little S, et al. (1999) Changes in blood lymphocyte populations after multiple trauma: association with posttraumatic complications. Crit Care Med 27: 733-740.

Citation: Zaghloul H, Abbas A (2017) The Pre-treatment Systemic Inflammatory Response Biomarkers are Important Determinant of Prognosis for Patients Undergoing Neoadjuvant Therapy for Rectal Cancer. J Cancer Sci Ther 9: 451-459. doi: 10.4172/1948-5956.1000458