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

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Abstract

Purpose: This research looks at inflammatory response biomarkers in the context of their prognostic potential, derived neutrophil to lymphocyte ratio (dNLR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) in patients suffering from rectal cancer and being administered neoadjuvant chemoradiation preceding surgical resection.

Methods: This work offers a retrospective review of "T3/T4, or N+ rectal cancer receiving neoadjuvant chemoradiation 50.4 Gy concurrently with either 5 FU (1 g/m2/d) or Capecitabine 825 mg/m2 twice daily. Pretreatment NLR, dNLR, PLR and LMR measured with the help of peripheral blood cell counts were correlated to clinicopathological parameters. Baseline NLR, dNLR, PLR and LMR prognostic value for disease free survival (DFS) and overall survival (OS) were studied through Cox regression and Log rank.

Results: This study revolved around 80 participants who had undergone resection subsequent to neoadjuvant chemoradiation. ROC or receiver operating curve cut off values for baseline were NLR (3), dNLR (2.1), LMR (4.9) and PLR(169). "Augmented NLR, dNLR, PLR, LMR , age ≥50 years , depth of invasion ≥T3 , lymph node N1-N2, stage III , grade 3 tumors, and partial response to pre-operative chemo-radiation were significantly correlated to reduced OS and DFS. A multivariate evaluation highlighted that risen NLR and dNLR stood as independent elements for worsened OS with an HR (hazard ratio) of 2.34 (95% CI= 3.41-7.24), 4.53 (95% CI, 2.61-8.32) and poor DSF with HR 1.64 (95% CI= 2.27-5.36), 4.23 (95% CI= 3.49-9.52), respectively."

Conclusion: The baseline inflammatory prognosticators revealed substantial link to various prognostic clinic-pathological parameters in the context of rectal cancer patients who had undergone neoadjuvant chemo-radiation. Moreover, both NLR and dNLR can be seen as possible independent indicators for prognosis in the given patient group.

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

Introduction

The fundamental curative treatment of rectal cancers which comprised one third of the whole colorectal cancer pool, is surgery that entailed total mesorectal excision [1,2]. Neoadjuvant chemo-radiotherapy is the authorized adjunctive modality in mesorectal fascia boundary-menacing rectal cancer. This method considerably ameliorated purging circumambient resection-sidelines consequently substantially minimizing risk of confined relapse [3-6]. The conventionally practiced extrapolative approaches based on presenting tumor burden were proved to be extremely restrictive in forecasting the outcome due to incongruity of prognosis in patients that were categorized to belong to the same clinical disease stage[7-9]. Additionally, the tremendous inconsistence in response to preoperative chemo-radiation (nCRT) amplified the necessity to explore innovative prognosticators that can accurately anticipate the destiny of rectal cancer patients . Lately, several peripheral blood indicators such as the neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte (LMR) have been authorized as extrapolative indicators in various kinds of cancers [12,13]. An amplified NLR was linked to abysmal consequences in colorectal cancer [14]. Meanwhile, PLR was perceived to be unreliable as a prognosticator based on its contradictory impact of outcomes as reported by the available body of evidence [15-18]. Nevertheless, antecedent researches scrutinized on the interaction of a maximum two of inflammatory cells driven prognosticators with outcmes[19-21]. Further to this, the optimal cut-offs for the designated indicators were encountered in studies that weren't consistent with regards to their prognostic potentials. Accordingly, supplementary authentication of the extrapolative modulation exerted by inflammatory prognosticators on clinical consequences is indispensable .Hence our conducted work delved into the collaboration of NLR, PLR, dNLR and LMR with various clinical-pathological variables alongside their survival modulation to forecast the outcome of rectal cancer patients managed with preoperative chemo-radiation.

Material and Methods

Records of rectal cancer patients managed Clinical Oncology department Alexandria University and Surgical Oncology department and National Cancer Institute Cairo University between January 2012 and December 2016, were reviewed to segregate eligible participants.

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The process was initiated after approvals were acquired from the Institutional Board Approval (IRB). The participants agreed to the study through informed consent, which they signed for. The records were reviewed to gather all clinical-pathological date of the rectal cancer patients managed with preoperative chemo-radiation. All laboratory work ups were revised to record the designated scores of pretreatment differential blood cells in addition to platelet counts. The extrapolative indicators 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.

We selectively included pathologically confirmed clinically staged T3/T4 and /or node positive rectal cancers. All participants the course of preoperative chemo-radiation that entailed 50.4 Gy in1.8 Gy fractions as whole pelvic radiation with concomitant 5-Fluorouracil (1 g/m2/d) as sustained 120 hours infusion during first and fifth weeks of radiation, or 5-Fluorouracil (400 mg/m2/d) and leucovorin 20 mg/m2 intravenous bolus for 4 days during the first and fifth weeks of radiation. Alternatively, Capecitabine 825 mg/m2 twice daily five days per week concurrent with radiation. Total mesorectal excision (TME) surgery was performed 4– 6 weeks after conclusion of preoperative CRT. Four additional cycles of 5-FU chemotherapy (500 mg/m2/d, i.v. bolus) or capecitabine (2500 mg/m2 days 1-14, repeated day 22), were applied postoperatively."

Assessment of Response to nCRT

RECIST criteria 1.1. was used to check radiologic response to therapy. It was outlined to be both primary tumor and lymph nodes downstaging as per 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. 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. On the contrary, we exempted patients who suffered from disseminated disease and those who had microscopic (R1) or macroscopic(R2) remaining disease postoperatively."

Follow up periods including (clinical exam, lab tests, imaging and endoscopy), stood between the 3 to 50 months and were arranged at 4-6 months interval.

Statistical Consideration

To inaugurate the extent of influence among intersected clinical-pathological variables including the verified prognosticators either Mann-Whitney U test (between 2 groups) or Kruskal- Wallis test (≥3 groups) were conducted. The receiver operator curves were devised to uncover the optimal thresholds of studied indicators in anticipating survival times. An area under the curve (AUC) of 1.0 would implied a significant test.

"Statistical informative levels stood at $P<0.05$. Log-rank test and Cox regression analysis were executed to associate clinical and pathological parameters to treatment outcomes. All analyses were performed using SPSS 16.0 package program, (SPSS, Chicago, IL)."

Results

The retrospective review of rectal cancer resulted in eighty patients managed with preoperative chemo-radiation followed by R0-TME with 54 (67.5%) men and 26 (32.5%) women while the median age stood at 52 years. The median values of baseline NLR, dNLR, LMR and PLR were 3.8, 3, 4.2 and 156 respectively. All baseline facets can be reviewed in (Table1). The NLR, dNLR optimal thresholds 3 (AUC:0.778) and 2.1(AUC:0.740) efficiently forecasted DFS with sensitivity (78.7%,77.3%) and specificity (85.3%,84.3%), respectively. In the same vein, LMR and PLR optimal cutoffs 4.9(AUC: 0.612) and169 (AUC: 0.545) recoded a sensitivity (68.7%,68.3%) and specificity (76.5%,68.3%), correspondingly (Figure1). Patients were subsequently allocated into two clusters centered on the optimal cut-off levels.

Different clinical-pathological elements were linked with the tested prognosticators. Correspondingly, the stage III denoting larger tumor sizes and more extensive infiltration of draining nodes were strongly interconnected to augmented scores of NLR, dNLR , LMR and PLR compared to lesser tumor burden tumors (Table 2)."

It is worth mentioning, that processing of postoperative specimens confirmed total disappearance of malignant cells from primary tumor bed and regional nodes (path CR) in 12.5% or 10 patients, whereas remaining malignant cells (path PR) were retrieved in (80%) or 64 participants. Therefore, the global response percentage stood at 92.5% i.e. 74 patients, whereas the leftover 6 patients, who accounted for 7.5%, demonstrated progressive or stable disease after preoperative chemo-radiation. All details of down staging were displayed in (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."

Several factors were ensuring pathological complete response as Tstage baseline, N stage baseline, and histopathological grade. The superior response was interconnected with lesser stage (P=0.002) and reduced baseline prognosticators NLR (P= 0.001) , d NLR(P= 0.002), LMR (P=0.001) and PLR(P=0.003), respectively(Table 4).

During follow up period, 32.5% or 26 patients were found to have distant metastasis or local recurrence. From this pool, 27.5% or 22 died from cancer-related complications. The OS and DFS median stood at 28 and 24 months, in that order. Further, the three-year overall survival stood at 72.5% while the disease-free survival registered at 67.5% (Figures 2 and 3). The detailed analysis of survival established that advanced stage, partial response to preoperative chemo-radiation (Figures 4 and 5) and augmented NLR (≥3), (Figures 6 and 7), dNLR (≥2.1) (Figures 8 and 9) , PLR (≥169), LMR (≥ 4.9) exhibited a strong link to worsened OS, and DFS (Table 5).

Multivariate scrutiny demonstrated that a accentuated baseline NLR and dNLR alongside advanced TNM stage at diagnosis were individually linked with abysmal OS, with hazard ratio 2.34 (95% confidence interval [CI], 3.41-7.24), 4.53 (95% CI, 2.61-8.32) and 4.21 (95% CI, 2.24-9.73), respectively. Similarly, worsened disease-free survival was profoundly attributed to augmented NLR, dNLR along with advanced TNM stage at diagnosis independently, with hazard ratio 1.64 (95% [CI], 2.27-5.36), 2.63 (95% CI, 2.61-8.12), 6.21 (95% CI, 1.28-14.23), respectively."

Discussion

The mediators instigated in tumor microevitoment through interaction with host native immune system orchestrates the chains of conditioning and sensitizing interaction of inflammatory cells both in tumor milieu and systemically in peripheral blood that reflect the proliferation of carcinogenesis. For instance, NLR, d-NLR, PLR and

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).

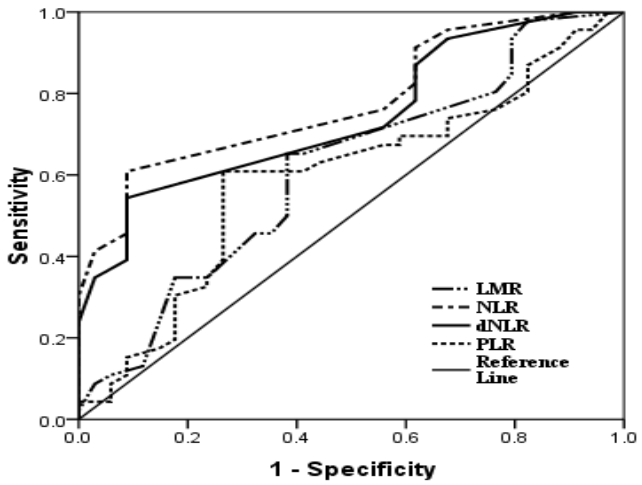

Figure 1: The receiver operator curve (ROC) of baseline NLR, dNLR, LMR, PLR in rectal cancer patients.

LMR that represented systematic indicators of inflammatory reactions induced by colorectal (CRC)malignancies in addition they operated as forecasters of outcome in CRC patients [23, 24].Consequently , the current work fundamental target was to emphasize the influence of baseline NLR , dNLR, PLR and LMR prognosticators in conjecturing the prognosis of rectal cancer patients undergoing preoperative chemo-radiation .The baseline NLR , dNLR , LMR and PLR forecasted DFS with informative areas under the curve(AUC) of 0.778 , 0.740, 0.612and 0.545 respectively . Similarly, Ying et al reported that preoperative NLR, d-NLR, PLR are robust prognosticators for colorectal cancer patients with ROC (AUC) of 0.764 , 0.672, 0.727 respectively . However, baseline LMR was exempted due to its non-significant AUC of 0.234 [25]. The discordance about the influence of baseline LMR can be principally attributed to the structure of studied population as we encompassed exclusively rectal cancer patients, while Ying et al enrolled both colon and rectal cancer patients in their analysis. Moreover, larger tumor burdens were strongly interconnected to augmented scores of NLR, dNLR, LMR and PLR compared to lesser tumor encumbrance. Ying et reached a resembling conclusion that accentuated baseline prognosticators were strongly attributed to advanced disease [25]."

As far as the authors of this study know, this is the first of its kind to successfully isolate cut off values for baseline biomarkers. "More importantly, superior responses were interconnected with lesser stage (P=0.002) and reduced baseline prognosticators NLR (P= 0.001), d NLR (P= 0.002), LMR (P=0.001) and PLR(P=0.003), respectively. It is imperative to mention that the results indicated advanced stage, partial response to preoperative chemo-radiation and augmented NLR (≥3), dNLR (≥2.1), PLR (≥169), LMR (≥ 4.9) exhibited a strong link to worsened OS, and DFS. On the other hand, multiple regression analysis showed that augmented baseline NLR, dNLR along with advanced TNM stage at diagnosis had independent correlation to shortened OS and DFS." In the same vein, Ying et al reported that elevated NLR, poorly differentiated tumors and larger tumor burdens stage were strongly interconnected with compromised OS and DFS [25]. The concordance established between the consequences of the current study and the prosperous body of evidence, emphasized on the forecasting influence of baseline prognosticators NLR, dNLR in rectal cancer patients curatively treated with preoperative chemo-radiation

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).

[26, 30]. The interaction of neutrophils with distinct malignant cell populations can be provoked by interleukin-6, tumor necrosis factor alpha and granulocyte colony-stimulating factor, myeloid growth factors. It subsequently stimulated an army of cytokines and effector molecules, such as circulating vascular endothelial growth factor (VEGF) which enhanced tumor angiogenesis, growth and metastasis [31-37]. Moreover, the tumor induced neutrophils amplification can suppress native cellular immunity by suppressing tumoricidal activity of cytotoxic CD8+ Tcells and accentuating T regulatory cells resulting in tumor proliferation [38,39].

The eloquence of the current work resides essentially on emphasizing the role of NLR, dNLR, PLR and LMR as potent prognosticators in rectal cancer managed with preoperative chemo-radiation. Moreover, the forecasting potential of the tested prognosticators was confirmed in a homogeneous population receiving consistent preoperative and surgical procedures. However, the retrospective scheme and limited number of participants were major contenders for absolute validation of our results and they necessitated further verification in a properly designed randomized trial.

Conclusion

The baseline inflammatory forcasters revealed substantial link to various prognostic clinic-pathological parameters in the context of rectal cancer patients who had undergone neoadjuvant chemo-radiation. Moreover, both NLR and dNLR can be seen as possible independent predictors for prognosis in the given patient group.7.

Conflict of Interest

The authors confirm that no funding or finances were acquired or received from the institutes that they share an affiliation with. The same is true for any external entities, including companies. Furthermore, the authors confirm that they had no conflict of interest to report in the context of this study.

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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.

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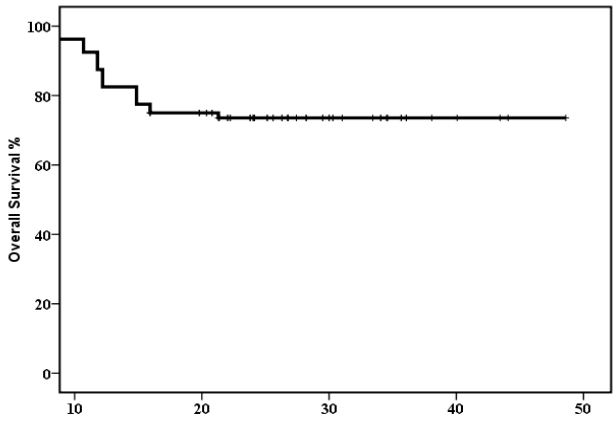

Figure 2: Overall Survival in months in rectal cancer patients treated with neoadjuvant chemoradiation.

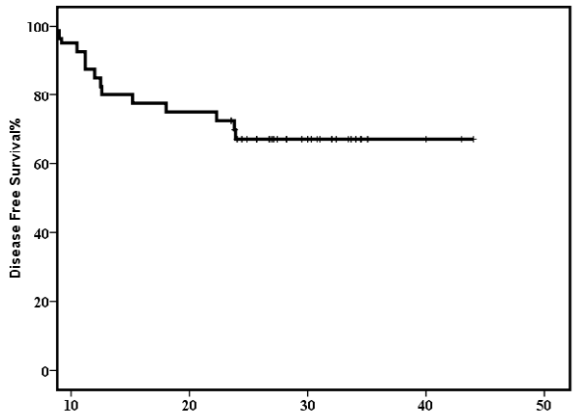

Figure 3: Disease free Survival in months in rectal cancer patients treated with neoadjuvant chemoradiation.

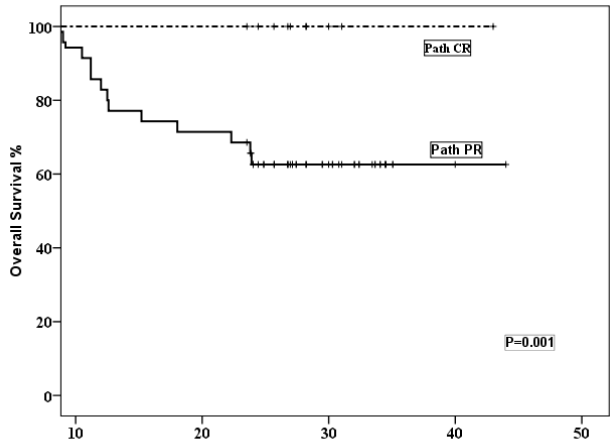

Figure 4: Overall survival by pathological response in months.

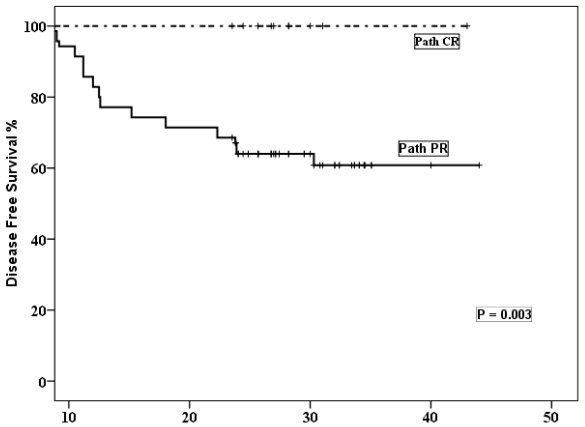

Figure 5: Disease free survival by pathological response in months.

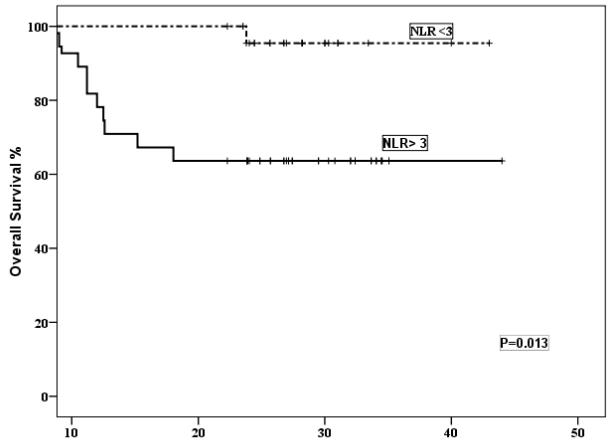

Figure 6: Overall survival by NLR cutoff level in months.

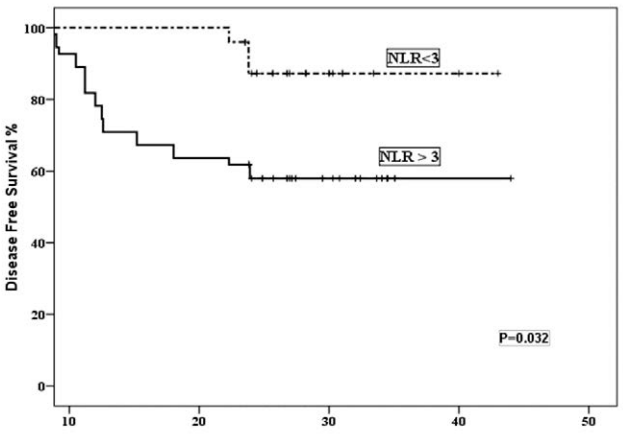

Figure 7: Disease free survival by NLR cutoff level in months.

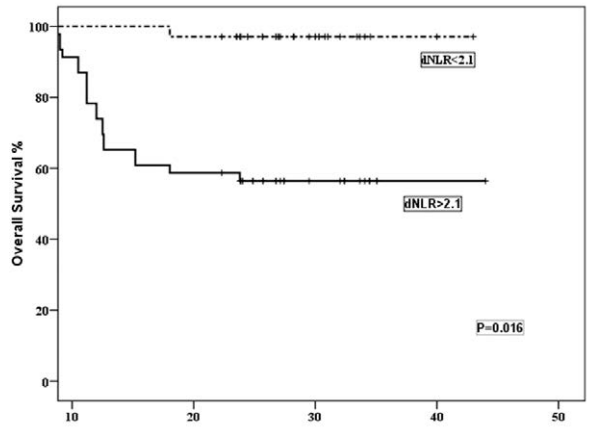

Figure 8: Overall survival by dNLR cutoff level in months.

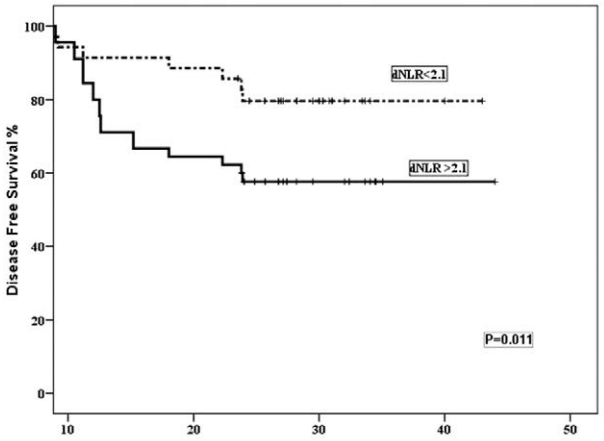

Figure 9: Disease free survival by dNLR cutoff level in months.

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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%)	**0.002***	6 (11.5%)	**0.011***
Moderately differentiated	56 (70%)	49 (84.5%)		44 (84.6%)	
Poorly differentiated	5 (6.3%)	2 (3.5%)		1(1.9 %)	
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%)	**0.003***	12 (23.1%)	**0.012***
T2	18 (22.5%)	18(31%)		17 (32.7%)	
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%)	**0.02***	18(34.6%)	**0.031***
N1	48 (60%)	36(62%)		32 (61.5%)	
N2	14 (17.5%)	4(7%)		2 (3.9%)	
Stage group at diagnosis					
IIA	8 (10%)	8(13.8%)	**0.01***	8 (15.4%)	**0.04***
IIB, C	10 (12.5%)	1 (1.7%)		0	
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%)	**0. 001***	10 (19.2%)	**0.003***
Partial response	64 (80%)	46 (79.3%)		42 (80.8%)	
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.

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