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ORIGINAL ARTICLE

# Neutrophil-to-lymphocyte ratio: a hidden gem in predicting neoadjuvant treatment response in locally advanced rectal cancer?

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## Summary

***Purpose:*** *The link between the pro-inflammatory status, tumor aggressiveness and treatment response has been well established in multiple cancers. Various hematologic and biochemical variables representing surrogates for inflammation have been used as predictive markers. Our primary aim was to assess the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in evaluating neoadjuvant treatment response in locally advanced rectal cancer (LARC).*

***Methods:*** *We included 60 consecutive patients with LARC, admitted for surgery, after completing a standard full-course neoadjuvant radio-chemotherapy regimen. NLR and other hematologic parameters were collected one day prior to surgery. Treatment response was assessed on the resection specimens.*

***Results:*** *On univariate analysis, poor responders had a significantly higher NLR value when compared with good responders: 5.81 (5.40-7.28) vs. 3.51 (2.36-4.04), p<0.0001. NLR retained its significance on multivariate analysis, with an OR of 3.51 (1.54-6.57), p=0.001. A NLR cut-off value of 4.50 had the best predictive value for poor response, with an area under the curve (AUC) of 0.85, sensitivity of 83.3% and specificity of 83.3% (p<0.001). Other hematologic ratios, such as the derived NLR (dNLR) and platelet-to-lymphocyte ratio (PLR) were also significant predictors for poor response, although to a lesser extent when compared to NLR.*

***Conclusion:*** *NLR is a simple and cost-effective predictor for neoadjuvant treatment response in LARC. As more data is generated, clear cut-off values could provide valuable insight regarding the management of LARC.*

***Key words:*** *complete pathologic response, neutrophil-to-lymphocyte ratio, nonoperative management, radiochemotherapy, rectal cancer*

## Introduction

Colorectal cancer currently accounts for approximately 10% of cancer[-] related mortality [1], and a significant percentage is attributed to rectal cancer (RC). The development of total mesorectal excision and neoadjuvant treatment in RC led to substantial improvement in tumor local control and overall survival. The standard of care in locally advanced rectal cancer (LARC) consists in neoadjuvant chemo-radiotherapy (CRT) followed by surgery after a delay of 8 to 12 weeks.

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Preoperative CRT can lead to a complete clinical response (cCR) rate varying between 10-40% and a complete pathological response (cPR) rate between 16-22% in patients with LARC, as demonstrated by a number of trials such as NSABP R-04 trial [2]. In early stage rectal cancer (T1-T2N0 tumors) the rate of cPR can be as high as 40-50% [3,4]. A cPR is associated with improved oncological results, as it represents the lack of tumor cells in the resection specimen. Thus, it offers the possibility of avoiding radical surgery and its associated functional consequences, stomas, morbidity and mortality [5,6].

Using the current available methods for clinical response evaluation, an overall survival (OS) rate of 89.9% and disease free survival (DFS) of 82.8% were observed for patients who underwent surgical management in comparison with 71.6% OS and 60.9% DFS for nonoperative management (NOM), suggesting the low accuracy for the prediction of pathologic response [7]. As such, routine use of NOM in a cCR patient is not yet recommended and new biomarkers are needed in order to improve the prediction of cPR.

Since 1986, when the link between the proinflammatory status, tumor progression and treatment response was hinted by Dvorak [8], multiple biochemical markers and hematologic parameters have been studied on different primary tumor locations [9]. Among them, high neutrophil count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and C-reactive protein (CRP) have been previously linked to disease progression, treatment response and overall survival in patients with colorectal cancer [10]. Newer ratios, such as derived neutrophil to lymphocyte ratio (dNLR), have also been proven to be effective predictors in certain clinical settings [11-17]. Although there are multiple studies addressing this topic, at the current time the cut-off values are equivocal and further data are needed in order to improve the predictive strength of these markers [18].

Our primary aim was to assess the role of NLR, calculated after standard full course chemo-radiotherapy, in predicting pathologic tumor response in patients with LARC. As secondary objectives, we analyzed the predictive value of two other ratios, PLR and dNLR, along with multiple other hematologic parameters.

## Methods

We conducted our study on a consecutive series of 60 patients with locally advanced rectal cancer who had previously received a standard full course of neoadjuvant chemo-radiotherapy. The patients were admitted in our department for surgery at 8-12 weeks after neoadjuvant treatment during a two-year timespan (2016-2018). Patient consent and local bioethics committee approvals were obtained. Pretreatment staging was performed using pelvic MRI or endorectal ultrasound. We included patients with cT3-T4 or cN positive - irrespective of cT staging. Patients who required emergency surgery were excluded, as well as patients with distant metastasis.

*Treatment protocol and yp staging*

All patients included in the study underwent radiation therapy with concurrent capecitabine /5-florouracil+oxaliplatin regimen. After treatment, the response (yp) was confirmed by assessing transmural invasion and nodal status according to the TNM classification. Complete pathological response was considered in patients with no tumor cells on histologic and immunohistochemical analysis of the surgical specimen according to Dworak tumor regression score [19]. Patients with cPR, partial response or downstaging were considered good responders (ypT0-T2, ypN0), while patients with high tumor burden or without downstaging were considered poor responders (ypT3-T4 or ypN1).

*Inflammatory markers*

Blood samples were obtained one day prior to surgery. White blood cell (WBC), neutrophil, lymphocyte, platelet and red blood cell (RBC) counts, hemoglobin,

**Table 1.** Clinical features of the study group

| *Features* | *Number (%) / Mean ± SD n (%)* |
|---|---|
| Age (years) | 62.9 ± 11.1 |
| Gender: female | 17 (28.33) |
| Distance from anal verge (cm) | 7.13 ± 3.29 |
| Surgical treatment | |
| Sphincter- sparing surgery | 42 (70) |
| Abdomino-perineal resection | 18 (30) |
| Complete resection (R0) | 54 (90) |
| ypT staging: | |
| T0 (complete pathologic response) | 11 (18.33) |
| T1 | 2 (3.33) |
| T2 | 11 (18.33) |
| T3 | 31 (51.70) |
| T4 | 5 (8.33) |
| ypN staging | |
| ypN0 | 40 (66.66) |
| ypN positive | 20 (33.33) |
| Lymphatic invasion (L1) | 9 (15) |
| Vascular invasion (V1) | 8 (13.33) |
| Perineural invasion (Pn1) | 7 (11.66) |
| Good response (ypT0-T2, ypN0) | 24 (40) |
| Poor response (ypT3-T4, yN+,CRM+, R+) | 36 (60) |

Continuous variables are shown as mean ± SD

hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were recorded. NLR was calculated as the neutrophil count divided by the lymphocyte count; PLR was calculated as the platelet count divided by the lymphocyte count. dNLR was calculated using the following formula: neutrophil count/(WBC-neutrophil count).

*Statistics*

Continuous data were expressed as either median and 95% confidence interval (CI) for skewed variables or mean±standard deviation (SD) for normally distributed variables. Skewed variables were compared using the Mann-Whitney U test.

Normally distributed variables were compared using the independent two-sample T-test. The NLR was correlated with the clinical and pathological variables using the chi-square test or Fisher's exact test. Variables with $p<0.05$ on univariate analysis were entered into multivariate analyses. Multivariate analysis to identify independent prognostic predictors was performed using Cox proportional hazard regression models.

Receiver operating characteristic (ROC) analysis was used for the prognostic accuracy of NLR in predicting treatment response and the value closest to the point with the maximum sensitivity and specificity was selected as the optimal cut-off value. Statistical analysis was performed using Medcalc v18.11.6.

## Results

The baseline characteristics of our cohort along with peri-operative data are summarized in Table 1.

*Pathological findings*

Complete resection (R0) was achieved in 90% of the cases. The rate of complete pathological response (cPR) in our study group was 18.3% (11 patients). Three patients with complete pathological response underwent APR and definitive colostomy. Patients with ypT3 tumors represented 51.7 %, while ypT2 and ypT1 represented 18.3% and 3.3%, respectively. Patients with ypT4 and no clinical response accounted for the remaining 8.3%. Twenty patients (33.3%) were ypN positive.

*Hematologic parameters*

According to neo-adjuvant treatment response, assessed via the pathology report of the resection specimen, the cohort was split in two groups: good responders and poor responders. The raw hematological parameters and the three predictive ratios (NLR, dNLR and PLR) were compared between the two groups. On univariate analysis (Table 2), neutrophil (4.78±1.24 vs. 3.33±1.51×$10^3$/μL, $p<0.001$) and white blood cell (6.33 ± 2.07 vs. 5.18 ±1.75×$10^3$/μL, $p=0.02$) counts were significantly higher in the poor response group. There were no significant differences regarding red blood cell and platelet counts between the groups. However, MCHC was significantly lower in the poor response group (32.96±1.46 vs. 34.10±1.20 g/dl, $p=0.003$). All three ratios assessed had a statistically significant increase in the poor response group. The strongest difference was encountered in the case of the NLR,

**Table 2.** Univariate analysis of pre- operative hematologic parameters according to tumor response

| *Hematologic parameters* | *Good response group Mean ± SD / Median (95% CI)* | *Poor response group Mean ± SD / Median (95% CI)* | *p value* |
|---|---|---|---|
| Neutrophils*, ×$10^3$/μL | 3.33 ± 1.51 | 4.78 ± 1.24 | **<0.001** |
| Lymphocytes**, ×$10^3$/μL | 0.88 (0.73-1.02) | 0.78 (0.55-0.94) | 0.14 |
| WBC*, ×$10^3$/μL | 5.18 ± 1.75 | 6.33 ± 2.07 | **0.02** |
| Platelets*, ×$10^3$/μL | 218.00 ± 70.12 | 242.19 ± 81.25 | 0.23 |
| RBC*, ×$10^3$/nL | 4.14 ± 0.48 | 4.26 ± 0.56 | 0.37 |
| Hemoglobin*, g/dl | 12.45 ± 1.19 | 12.15 ± 1.95 | 0.51 |
| MCV**, fl | 87.6 (86.09-91.10) | 86.25 (81.05-89.22) | 0.18 |
| MCH*, pg | 29.91 ± 2.66 | 28.54 ± 3.21 | 0.08 |
| MCHC*, g/dl | 34.10 ± 12 | 32.96 ± 1.46 | **0.003** |
| NLR** | 3.51 (2.36-4.04) | 5.81 (5.40-7.28) | **<0.0001** |
| dNLR** | 2.01 (1.42-2.60) | 2.63 (2.18-3.14) | **0.01** |
| PLR** | 228.61 (199.89-302.69) | 295.61 (254.24-430.57) | **0.02** |

Continuous variables are shown as mean ± standard deviation* (normally distributed) or median** (95% confidence interval), for skewed variables; WBC–white blood cell count, RBC–red blood cell count, MCV–mean corpuscular volume, MCH–mean corpuscular hemoglobin, MCHC–mean corpuscular hemoglobin concentration, NLR–neutrophil to lymphocyte ratio, dNLR–derived neutrophil to lymphocyte ratio, PLR–platelet to lymphocyte ratio. Bold numbers denote statistical significance.

with a 5.81 (5.40-7.28) score in the poor response group, compared to 3.51 (2.36-4.04) for the good responders (p<0.0001).

The variables with significant differences on univariate analysis were included in a multivariate regression (Table 3). The raw hematologic counts, already included in the three ratios were not included in order to prevent variable overlap. NLR retained its significance as an independent predictor for poor response, with an OR of 3.16 (1.54-6.57), p=0.001. Normal MCHC values appeared to be independent protective factors against poor response, with an OR of 0.49 (0.27-0.89), p=0.02. The other two hematologic ratios, dNLR and PLR did not retain statistical significance on multivariate analysis.

Furthermore, patients were split into a high NLR and low NLR group, based on a cut-off value

**Table 3.** Multivariate analysis of pre-surgery hematologic parameters according to tumor response

| *Hematologic parameters* | *Odds ratio* | *95% confidence interval* | *p value* |
|---|---|---|---|
| NLR | 3.16 | 1.54-6.47 | **0.001** |
| dNLR | 1.15 | 0.67-1.98 | 0.59 |
| PLR | 0.99 | 0.98-1.00 | **0.15** |
| MCHC | 0.49 | 0.27-0.89 | **0.02** |

NLR–neutrophil to lymphocyte ratio; dNLR–derived neutrophil to lymphocyte ratio; platelet to lymphocyte ratio, MCHC–mean corpuscular hemoglobin concentration. Bold numbers denote statistical significance.

**Table 4.** Comparison between the High-NLR group and the Low-NLR group according to clinical, histological and therapy-related parameters

| *Variables* | *High-NLR group* | *Low-NLR group* | *p value* |
|---|---|---|---|
| Number of patients (%) | 35 (58.33%) | 25 (41.66%) | |
| Age* | 62.0 ± 12.8 | 64.3 ± 8.4 | >0.05 |
| cPR (T0) | 2 (5.71%) | 9 (36%) | 0.008 |
| ypT1-T2 | 3 (8.57%) | 11 (44%) | 0.003 |
| ypT3-T4 | 31 (88.7%) | 5 (20%) | <0.0001 |
| ypN positive | 17 (48.5%) | 3 (12%) | 0.007 |

Continuous variables are shown as mean ± standard deviation* (normally distributed) or for skewed variables; cPR - complete pathological response

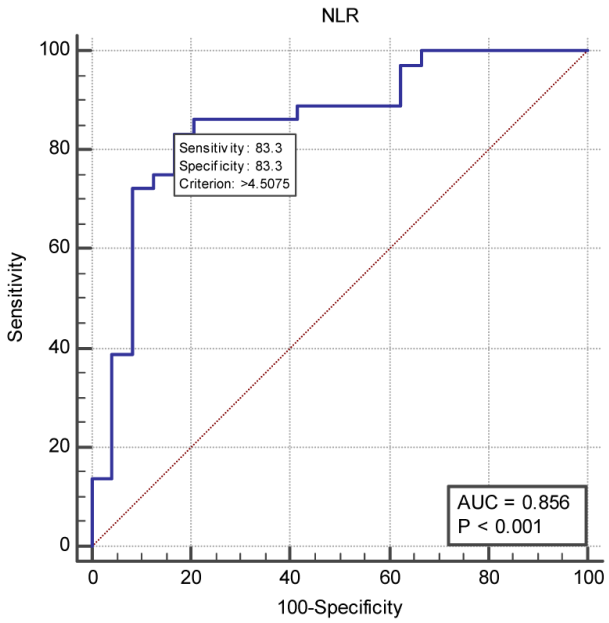


**Figure 1.** AUROC curve analysis for NLR AUC: area under curve; NLR: neutrophil to lymphocyte ratio.

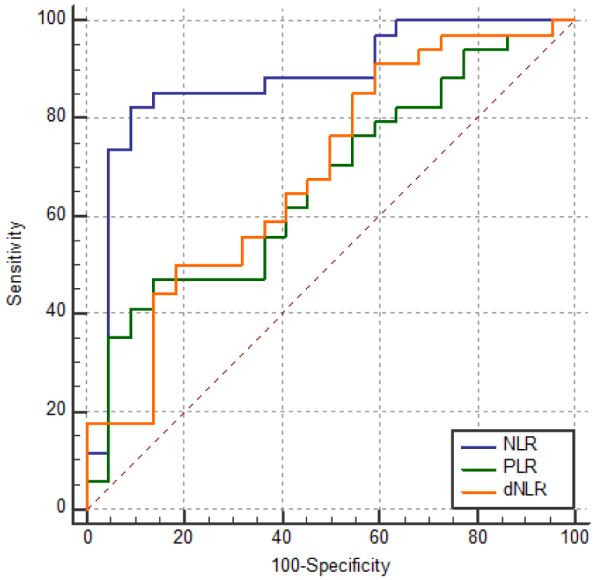


**Figure 2.** AUROC curves comparison for NLR, dNLR and PLR. NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio; dNLR: derived neutrophil to lymphocyte ratio.

of 4.5. This cut-off value was chosen based on the AUROC analysis, as the value closest to the point of maximum sensitivity and specificity. The resection specimens were consequently analyzed. The high NLR group had significantly more locally advanced tumors. Lymph node invasion was more common in the high NLR group. This comparison is summarized in Table 4.

We analyzed the AUROC curves for the three hematologic ratios. NLR had the best predictive value for poor response, with an AUC of 0.85, sensitivity of 83.3% and specificity of 83.3% for the cut-off value of 4.50 ($p<0.001$), as shown in Figure 1. PLR had an AUC of 0.67, sensitivity of 47.2% and specificity of 87.5% for a cut-off value of 338.37 ($p=0.012$). dNLR had an AUC of 0.69, sensitivity of 91.2% and specificity of 40.9%, using 1.55 as a cut-off ($p=0.01$). The comparison between the aforementioned curves is illustrated in Figure 2.

## Discussion

To answer our main objective, we found that pre-operative NLR was a strong independent predictor for poor response to neoadjuvant chemo-radiotherapy when using a cut-off value of 4.5.

Surgery affects the quality of life (QoL) in patients with rectal cancer [20,21]. In 2004, Habr Gamma et al reported promising results for patients with complete clinical response and proposed the NOM of rectal cancer [22]. Since then, some publications showed encouraging results but there is a lack of prospective randomized trials.

Currently, the complete clinical response is assessed using digital rectal examination, endoscopy and imaging studies. Clinical assessment should be performed at 8-12 weeks after completing the preoperative treatment, when a possible complete response will reach the maximum probability. Endoscopy will show pale mucosa or telangiectasia. Biopsy can be used as an adjunct, but it may miss up to one third of the patients with deep persistent tumor cells [23]. The restriction of the diffusion during diffusion-weighted MRI in the rectal wall or mesorectum should be highly suspicious of residual tumor [24,25]. Furthermore, molecular imaging studies such as PET/CT provide detection rates of up to 85%, but may not be suitable (significant irradiation) and available for routine use [26].

The assessment of cCR is highly subjective and may not predict the cPR with the highest accuracy. As a result, the OS of the patients might be impaired: studies report an OS rate of 87.6% in pCR vs. 75.4% in cCR who experience recurrence after NOM. Changes in tumor phenotype due to treatment will result in rapidly growing tumor and aggressive biological behavior. If salvage surgery is possible, local control can be achieved in up to 94% of the patients [27].

NLR above 5 has been demonstrated by Walsh et al on 230 patients with colorectal cancer to be related to poor oncological outcome in terms of survival and disease control [28]. Moreover, Kim et al [12] reported similar results in patients with LARC who received preoperative radio-chemotherapy and had a pretreatment NLR above 3. According to the studies published so far, a higher NLR result in higher pro-tumor activity which will affect the oncological outcomes of the patient [13].

In the current study we included rectal cancer patients who underwent preoperative chemo-radiotherapy. The NLR was calculated before surgery, after completion of neo-adjuvant treatment. The cut-off value of NLR was 4.5, similar with NLR of 5 reported by Walsh et al [28]. A higher NLR ratio seems to be associated with a high tumor burden. In our study, the complete response was significant for NLR<4.5. The predictive accuracy of NRL>4.5 for poor chemo-radiotherapy outcome was 0.85 with a sensitivity of 83.3%, specificity of 83.3 %, $p<0.01$. No data is available yet regarding disease free survival and overall survival, but Kim et al [12] reported unfavorable outcomes in patients with NLR above 3. In our study group, 88.7% of the patients with NLR above 4.5 showed poor response to neoadjuvant CRT and 48.5% presented residual nodal disease.

As secondary aims in our study, we analyzed the predictive value of other hematologic ratios, such as PLR and dNLR. While their predictive powers could not match NLR on our cohort, we found a clear, significant correlation with poor response on univariate analysis. However, their low sensitivity or specificity rendered them difficult to interpret as prognostic factors. Our findings are consistent with other data in the literature. Regarding PLR, one study with a similar design found an AUC of .674, 95% CI .592–.756, sensitivity 63.2% and specificity 62.9% ($p<0.001$) [10]. dNLR was initially developed as a surrogate for NLR in settings in which lymphocyte counts were not available for various reasons. On a large retrospective analysis [13] dNLR was similar to NLR as a mortality predictor on a heterogeneous oncological population. However, in our specific setting we did not find the same correspondence between the two ratios.

Our approach had several limitations. We did not include a dynamic assessment of the hema-

tologic variables in order to analyze the inflammatory burden at the beginning of neo-adjuvant treatment. Furthermore, we did not include post-surgical follow-up data. Nevertheless, data from our resection specimens were encouraging and should be closely correlated with overall prognosis.

Surgical resection remains the standard of care in rectal cancer in the lack of unquestionable evidence for NOM strategies in cCR patients. As of now, patients who prefer NOM or are unfit to surgery must be well informed regarding the potential benefits and harms of NOM [29].

The relationship between the host immune system and tumor microenvironment is of high complexity and most probably a single marker will not be able to offer a perfect response. Although NLR is correlated with a high tumor burden, it may not determine the response to neoadjuvant CRT and it is more likely a surrogate for the interaction between the host immune system and tumor microenvironment [30].

## Conclusion

Post-neoadjuvant therapy NLR below 4.5 is associated with partial or complete pathologic response in patients with advanced rectal cancer. A NLR above 4.5 predicts poor response or no response at all and residual lymph node invasion. Although a cautious approach is needed, NLR should be taken into account when selecting clinical complete response patients for non-operative management as it may increase the accuracy of current clinical assessment methods.

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## Conflict of interests

The authors declare no conflict of interests.

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