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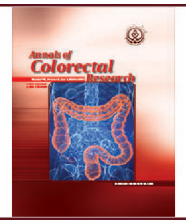

Factors Associated with a Higher Rate of Pathological Complete Response After Long-Course Neoadjuvant Treatment for Locally Advanced Rectal Cancer Patients – Results from a Retrospective Cohort Study Focused On Inflammatory Indices

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Abstract

Background: Pathologic complete response (pCR) after neoadjuvant chemoradiotherapy (NCRT) has a prognostic value in locally advanced rectal cancer (LARC). This study aimed to evaluate the ability to predict pCR using inflammatory markers, facilitating the selection of the optimal treatment strategy.
Methods: Patients undergoing primary tumor resection after long-cycle NCRT at a single center (2012 to 2018) were retrospectively collected (n=130). Patient demographics, preoperative laboratory measurements, tumor characteristics, treatment strategy, and postoperative anatomopathological variables were collected. The association of factors to pCR was examined using binary logistic regression, odds ratio (OR) (95% confidence interval), and the discriminative capacity with the ROC curve.
Results: Out of 130 patients, 42 pCRs occurred, equal to 32.3% of the sample. Variables identified as useful to predict pCR were total neutrophil count (<6400 cells/mm^3; OR 7.6), intravenous 5-FU chemotherapy strategy (OR 3.2), and absence of diabetes (OR 3.4). Patients having all three of them had a 55.3% chance of pCR.
Conclusion: The absolute neutrophil count better predicts pCR than other inflammatory indices in selected patients with LARC undergoing long-cycle NCRT. A neutrophil count less than 6400 cells/mm^3, absence of diabetes, and intravenous 5-FU NCRT therapy lead to a relative rise in pCR.

Keywords: Pathologic complete response, Neoadjuvant chemoradiotherapy, Inflammatory indexes, Neutrophil, Rectal cancer, Tumor regression

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Introduction

Colorectal cancer remains a leading cause of cancer death worldwide, representing the third most commonly diagnosed cancer and the second cause of cancer-related mortality (1). In locally advanced rectal cancer (LARC) patients, preoperative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is considered the standard treatment approach to reduce local recurrence and prolong the disease-free survival (2). However, several other strategies might be employed and are currently being investigated (3-5).

Complete pathologic response (pCR) or regression degree in LARC after CRT occurs in up to 35% of patients (6, 7) and is considered a prognostic factor of the disease (8, 9). To date, the absolute count of inflammatory and hematologic markers such as neutrophils (10, 11) or platelets (11), and several inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have been investigated as long-term survival prognostic biomarkers (12-22), as well as the ability to predict the pCR after neoadjuvant CRT (NCRT) and posterior TME surgery (7, 23, 24).

The interest in obtaining accurate predictive markers is high as it allows us to select the most appropriate patients to provide with each kind of therapy. We aim to offer maximal benefits with minimum drawbacks (e.g., adverse effects and toxicity). To this end, further investigations are needed, especially in those scarcely studied issues such as inflammatory markers.

Our study aimed to determine the pCR rate obtained at our institution and analyze possible predictive factors like the pre-neoadjuvant inflammatory markers and ratios.

Materials and Methods

Patients

For the present study, the institutional prospectively maintained database for rectal cancer was studied from January 2012 to December 2018.

Patients met the following inclusion criteria: 1) histologically confirmed adenocarcinoma; 2) LARC (T3N0 or any T N+) diagnosed with pelvic magnetic resonance imaging (MRI); 3) long-cycle NCRT; 4) complete radical resection with curative intention. Patients with an emergency presentation or surgical intervention (long-cycle NCRT not completed), metastatic disease at diagnosis, T4 stage, or sphincter invasion were excluded from the present analysis as these are independent factors associated with a lack of pCR (25-27). Figure 1 shows the study cohort after inclusion and exclusion criteria were scrutinized.

The Local Clinical Research Ethics Committee approved the study.

Variables

Patients´ demographics, relevant past medical history and treatments, preoperative laboratory measurements, preoperative (MRI) tumor characteristics, preoperative treatment, intervention procedure, postoperative anatomopathological characteristics, and pathologic response reports according to American Joint Committee on Cancer (AJCC) Staging Manual (24) were collected.

Laboratory measurements

Patient blood samples were obtained within one week before the start of NCRT.

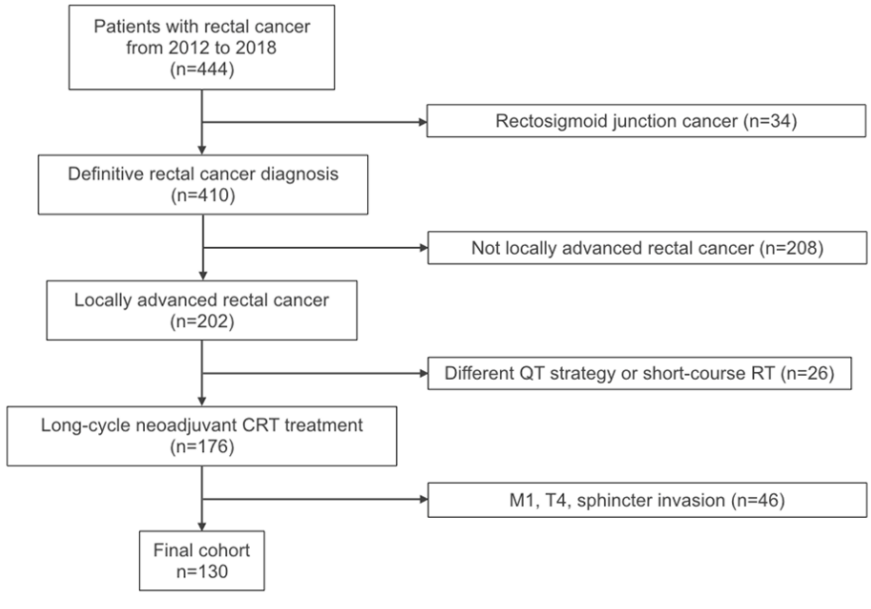

Figure 1: Flowchart of patients' cohort based on inclusion and exclusion criteria. CRT: chemoradiotherapy; QT: chemotherapy; RT: radiotherapy.

The most commonly studied inflammatory rates were calculated, namely NLR, LMR, and PLR.

MRI Protocol

A 1.5 T scan was used. The study protocol included T2-weighted sequences and diffusion-weighted imaging (DWI) with 3 mm slices. For mid and low rectal cancer tumors, endorectal gel was used.

Chemoradiotherapy administration

Long-cycle NCRT consisted of combined radiation (180 cGy, five days a week for five weeks, followed by a 540 cGy boost) and chemotherapy, either oral capecitabine (CAP) or 5-fluorouracil

Table 1: Clinicopathologic factors, pre-treatment analytical variables, and type of neoadjuvant chemotherapy of 130 patients with and without pathological complete response (pCR).

	Total n=130	pCR n=42	No pCR n= 88	P value
Demographic variables				
Age*	66 (59-75)	67 (61-74)	66 (59-75)	0.756
Sex (male)	87 (66.9)	26 (61.9)	61 (69.3)	0.401
Comorbidities				
Hypertension	68 (52.3)	19 (45.2)	49 (55.7)	0.265
Diabetes	31 (23.8)	5 (11.9)	26 (29.5)	0.027
Cardiopathy	10 (7.7)	1 (2.4)	9 (10.1)	0.116
COPD	10 (7.7)	2 (4.8)	8 (9.1)	0.386
Hepatopathy	4 (3.1)	1 (2.4)	3 (3.4)	0.751
Nephropathy	5 (3.8)	1 (2.4)	4 (4.5)	0.548
Tobacco use	19 (14.6)	6 (14.6)	13 (14.6)	0.677
Enolism	17 (13.1)	6 (14.3)	11 (12.5)	0.778
MRI variables				
T MRI				
cT2	5 (3.1)	2 (1.5)	3 (2.3)	0.708
cT3	126 (96.9)	40 (98.5)	86 (97.7)	
N MRI				
cN0	12 (14.1)	4 (7.1)	8 (16.5)	0.918
cN1	78 (60.0)	25 (61.0)	53 (59.6)	
cN2	41 (31.5)	13 (31.7)	28 (31.5)	
Distance from anal verge (cm)*	7.4 (6.8-7.9)	6.8 (5.6-8.2)	7.7 (5.7-9.1)	0.33
Tumor size (cm)*	4.5 (4.0-6.0)	4.8 (3.8-6.0)	4.5 (4.0-6.0)	0.856
Circumferential extension				
<25%	5 (3.1)	2 (1.5)	3 (2.3)	0.692
25–50%	37 (28)	15 (35.9)	22 (24.4)	
50–75%	25 (19.2)	7 (17.9)	17 (19.8)	
>75%	63 (51)	18 (45)	46 (52.3)	
Analytical variables				
Neutrophil count*	4760 (3820-6125)	4525 (3040-5805)	5085 (4070-6285)	0.030
Monocyte count*	625 (477-755)	585 (477-750)	645 (465-780)	0.430
Lymphocyte count*	2135 (1330-2785)	1960 (1270-2725)	2170 (1382-2852)	0.508
Platelet count*	237 (194-287)	224 (185-286)	241 (199-293)	0.205
NLR	3.2 (2.4-4.3)	3.2 (2.3-4.4)	3.3 (2.4-4.5)	0.731
LMR	2.3 (1.8-3.2)	2.3 (1.7-2.9)	2.4 (1.8-3.2)	0.446
PLR	122 (84-177)	125 (84-180)	120 (85-176)	0.911
Neoadjuvant chemotherapy				
IV 5-FU	77 (59.2)	31 (73.8)	46 (52.3)	0.019
Oral Capecitabine	53 (40.8)	11 (26.2)	42 (47.7)	
Sphincter preservation rate				
TME + anastomosis	103 (79.2)	36 (85.7)	67 (76.1)	0.31
Hartmann´s procedure	8 (6.2)	1 (2.4)	7 (8)	
APR	19 (14.6)	5 (11.9)	14 (15.9)	
Surgical margin				
Free circumferential margin	129 (99.2)	42 (100)	87 (98.8)	0.67
Free distant margin	128 (98.5)	42 (100)	86 (97.7)	0.45

Values as median (IQR) or n (percentage). pCR=pathological complete response; COPD=chronic obstructive pulmonary disease; MRI=magnetic resonance imaging; T=tumor; N=nodal; NLR=neutrophil-to-lymphocyte ratio; LMR=lymphocyte-to-monocyte ratio; PLR=platelets-to-lymphocytes ratio; IV 5-FU=intravenous 5-fluorouracil. *Neutrophil, monocyte, and lymphocyte counts: cells/mm^3; platelet count: x10^9/L; TME: total mesorectal excision; APR: abdominoperineal resection

(5-FU) continuous intravenous infusion regimen. Capecitabine dose was 850 mg / m^2 twice daily every day that radiotherapy was administered, and the dose of continuous infusion of 5-FU was 300 mg/m^2 daily, five days each week.

The selection of oral capecitabine or 5-FU infusion was made based on patients´ clinical characteristics and 5-FU adverse effects.

Waiting time for surgery after the completion of NCRT at our institution was eight weeks.

Definition of pCR

In this study, pCR (ypCR/ypT0N0Mx) is defined as the total absence of any tumoral cell along the rectal wall, mesorectal fat, or any of the isolated lymph nodes in the TME specimen.

Statistical Analysis

Variables and their association with pCR (ypT0N0M0 in the surgical sample after neoadjuvant CRT) were analyzed. Continuous variables (non-normal distribution Kolgomorov-Smirnov test) were described as median (interquartile range [IQR]) and categorical variables as percentages. For comparisons between groups, the Mann-Whitney test was used for continuous variables, while the chi-squared test (Fisher's test when needed) was used for categorical variables.

Two multivariable models of pCR prediction were built. One was the Classification and Regression Trees (CART) model, with internal cross-validation (10 folds) and stop criteria and a minimum number of subjects in the terminal nodes of 5. The other was the multiple binary logistic regression (LR) model with the calculation of odds ratio (OR) (95% confidence interval [CI]) (25). In multivariate models, variables were introduced with a full-model strategy and automatic step selection. The discriminative capacity was evaluated with ROC methodology (area under the curve [AUC]; CI 95%).

A value of P<0.05 was considered statistically significant. Statistical analysis was performed using the IBM SPSS Statistics v25.0 software and CART model with the Answer Tree module.

Results

A total of 130 patients were included in the analysis, including 87 males (66.9%) and 43 females (33.1%), with an average age of 66 years. The clinicopathologic factors and their association with pCR were analyzed (Table 1). A total of 42 pCRs occurred, equal to 32.3% of the sample. The absence of diabetes (P=0.027) was found an independent statistically significant favorable factor for pCR to occur. Age, sex, other comorbidities, and pretreatment tumor variables including lymph nodes' involvement, tumor size, and circumferential extension were not associated with pCR. Among the pre-treatment analytical variables, the only factor independently associated with pCR was the absolute neutrophil count (P=0.030), whilst the absolute platelet count (P=0.205), the NLR (P=0.731), LMR (P=0.446), and PLR (P=0.911) did not show statistical significance. A significant relationship was also established between the use of intravenous 5-FU (instead of oral capecitabine) and pCR (P=0.019).

The discriminatory capacity of the analytical variables (neutrophils, lymphocytes, monocytes, and platelets' absolute counts) and NLR, LMR, and PLR ratios and their diagnostic efficiency for pCR were analyzed by ROC curves (Figure 2). The absolute count of neutrophils was the only variable that showed a discriminatory capacity with an AUC=0.62 (0.52-0.72).

The optimal cutoff value of the absolute neutrophil count was 6400 cells/mm^3, determined through the CART model (Figure 3). On multivariate pCR analysis, the variables identified as independently associated with pCR were the total neutrophil count (<6400 cells/mm^3) (OR 7.6 [1.6-35.2]), the use of 5-FU chemotherapy (OR 3.2 [1.4-7.5]) and the absence of diabetes (OR 3.4 [1.2-10.2]). Patients presenting the three favorable variables were found to have a 55.3% chance of pCR (Table 2).

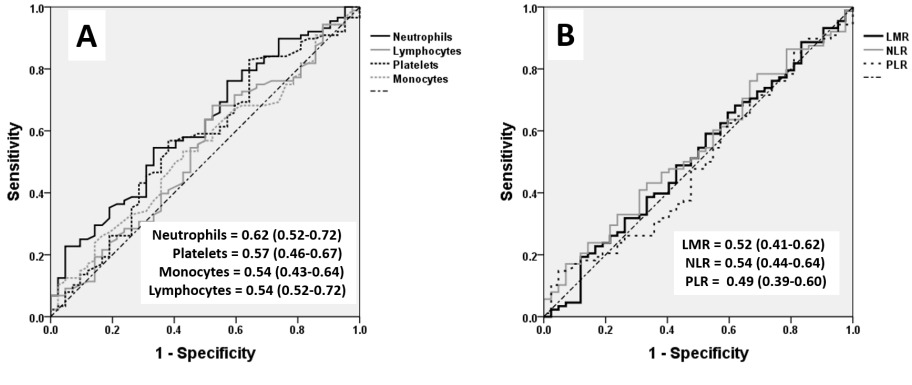

Figure 2: ROC curves comparing predictive values for PCR. (A) Neutrophil, lymphocyte, monocyte, and platelet absolute counts. (B) NLR, LMR, and PLR inflammatory indices. Values=AUC (CI 95%).
NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.

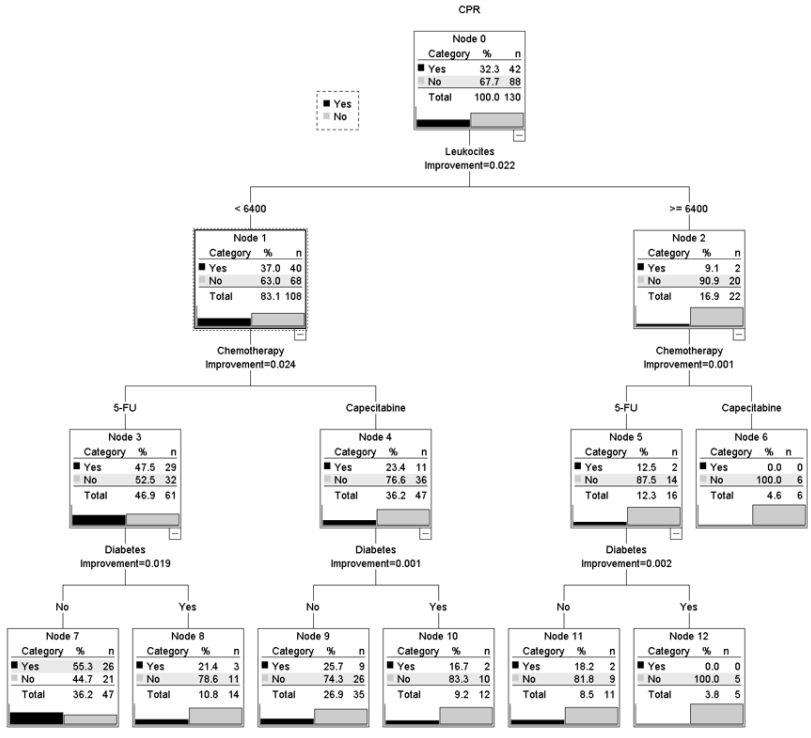

Figure 3: Classification and Regression Trees (CART) model for predicting complete pathological response (CPR). 5-FU: 5-Fluorouracil.

Table 2: Multivariate binary logistic regression model of pathological complete response.

Predictor	OR	CI 95 %	P value
No diabetes	3.4	1.2–10.2	0.024
Neutrophil count <6400/mm^3	7.6	1.6–35.2	0.010
Chemotherapy with endovenous 5-FU	3.2	1.4–7.5	0.007

OR=odds ratio; CI=confidence interval

The capacity of CART and LR models in terms of diagnostic efficiency for pCR was evaluated through ROC curves (Figure 4) (CART=0.73 [0.64-0.82]; LR=0.76 [0.67-0.85]).

Discussion

The prognostic significance of systemic inflammatory response and its association with tumor progression

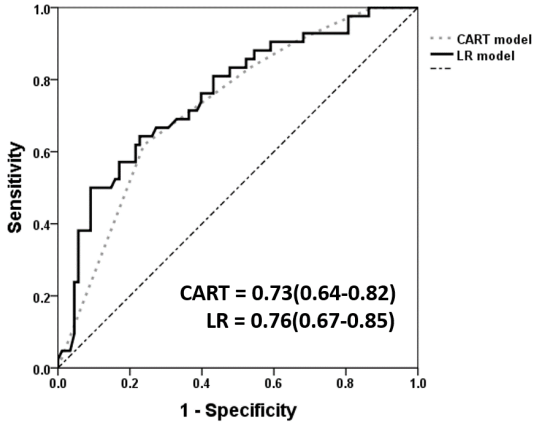

Figure 4: ROC curves comparing predictive values for complete pathological response. Values=AUC (CI 95%). CART: Classification and Regression Trees; LR: Logistic Regression.

reveals the potential of predicting neoadjuvant chemotherapy outcomes depending on the patient's systemic inflammation pretreatment status (12, 19). This promising association has prompted many investigations to be carried out on different biomarkers and indices such as the absolute count of neutrophils (6, 7) and platelets (7), the NLR, LMR, and PLR (8-10). Such studies aim to convert this issue into a useful everyday tool for determining whether a more patient-individualized therapy could be planned with a simple and inexpensive blood test.

Out of the whole cohort in our study, a 32.3% pCR was obtained, consistent with similar described series (3, 26, 27) in terms of inclusion and exclusion criteria, NCRT strategy, and surgery, with reported pCR rates of 25-35%.

This study showed that the only inflammatory marker that was independently associated with pCR after NCRT in LARC was the absolute neutrophil count.

Accumulating evidence has shown the NLR to be a strong predictor of poorer prognosis, tumor recurrence, and decreased overall survival (11, 13, 16-18). However, the findings in the present study are consistent with the report of Watt et al. (6), who associated the prognostic value of NLR

to the absolute neutrophil count, which alone had a stronger prognostic value than the lymphocyte count or the NLR. They correlated the neutrophils' superior prognostic value with its primarily up-regulation of the innate immune system, better reflecting the basis of the systemic inflammatory response (6, 28). Correlatively, Policicchio et al. (7) described the possible predictive value of the combination of higher platelet and neutrophil counts at the time of diagnosis. Furthermore, the present study is consistent with Ramsay et al. (29). They, in 330 patients, observed no prognosis prediction in calculating ratios, finding the total white cell count or the neutrophil count to be better predictors of pCR in NCRT. When comparing research papers, design variability (different inclusion and exclusion criteria, sample number, etc.) is a limitation. Limited research has been conducted to compare the three most studied systemic inflammatory ratios (NLR, LMR, and PLR) to the absolute neutrophil count. The results of the current study show the superiority of the latter and could have implications for the prognostic value of pCR after NCRT in LARC.

Another main finding of our study was that the absence of diabetes could play a role in the prediction of pCR. This is consistent with Yu et al. (30) and Caudle et al. (31), who revealed that not having diabetes was an independent predictive factor of pCR after CRT and that CRT in rectal cancer was less effective in diabetic patients. This could be explained due to the immunosuppressive effect of diabetes, resulting in impaired innate and acquired immunity (32). In a different line of reasoning, Oh et al. (33) described an association between metformin use and significantly higher pCR rates as well as improved survival. Also, Kim JM et al. (34) determined a connection between the use of metformin in diabetic patients and better tumor responses, cancer-specific survival, and lower risk of cancer recurrence in patients who had lymph node downstaging after NCRT, consistent with Skinner et al. (35), who concluded higher tumor response rates to radiotherapy in diabetic patients using metformin (36-39). These findings indicate the advantage of a lack of diabetes and the importance of metformin use in diabetic patients in terms of pCR.

On the other hand, the use of 5-FU as chemotherapy (CT) rather than CAP as a better pCR prognostic predictor could be explained due to its intravenous administration and more constant and stable dose than the oral administration of CAP and its fluctuating concentrations. Nevertheless, our findings are not consistent with the meta-analysis performed by Chen et al. (2), who determined that the use of CAP or oxaliplatin had a significantly higher rate of pCR compared to 5FU. As this was not the main focus of our research, the well-founded reasons are beyond the scope of this study and should be further investigated. However, according to our findings, using 5-FU as CT had a determinant significance when associated with the absence of diabetes and less than 6400 neutrophils/mm^3, as having the three of them meant a 55.3% chance of pCR.

Neither the impact of the association between factors nor such a high pCR value was found in recent literature. If not contrasted by future prospective research, these unprecedented findings would have relevant clinical implications when determining the most appropriate and individualized therapy in terms of NCRT in patients with LARC. In addition, predictors of pCR should be considered in the research of complete or nearly complete clinical response in organ preservation strategies (40, 41).

Limitations of the present study include its retrospective and single-center nature, strict inclusion criteria, and the relatively small number of patients (n=130), which may have resulted in bias during statistical analysis.

Conclusion

This study shows the superiority of the absolute neutrophil count compared to the platelet count, NLR, LMR, and PLR indices as a pCR prognostic predictor after NCRT in patients with locally advanced rectal cancer, especially when associated with a lack of diabetes and the 5-FU chemotherapy strategy. Assessment of preoperative neutrophil count is a standard, widely available, and inexpensive biomarker that can help physicians identify patients with a potentially greater benefit of NCRT strategy, as well as being useful in those cases in which the application of NCRT is considered doubtful, promoting the use of the most appropriate and least harmful treatment in patients with locally advanced rectal cancer.

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Conflicts of interest: None declared.

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