Systemic inflammation-based predictors of pathological response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer patients: A propensity score matching analysis

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Research

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Abstract

Background: In the management of locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy (CRT), the relationship between systemic inflammation-based predictors and tumor response remains unclear. This study aimed to determine whether these inflammatory factors can predict tumor response.

Methods: Totally 205 LARC patients underwent neoadjuvant CRT and curative surgery between 2008 and 2017 were analyzed. After propensity score matching, 146 patients (73 matched pairs) were enrolled in this study. The hematological parameters were collected and their relationship with tumor response was investigated.

Results: After propensity score matching, the neutrophil-lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR) before CRT in good response group were significantly lower than those in poor response group, while there was no significant difference in all hematological characteristics between two groups after CRT. The cutoff values of pre-CRT NLR and pre-CRT PLR were 3.10 and 198.7 after receiver operating characteristic analysis. Multivariate analysis model indicated that pre-CRT PLR was not related with tumor response, while pre-CRT NLR≥3.1 was the predictor of poor tumor response (OR=2.047, 95%CI =1.241-3.377, p=0.005). Besides, patients with NLR≥3.1 had a significantly poor tumor regression grade rates compared with patients with NLR<3.1 (p=0.036).

Conclusion: The increased NLR before CRT can be regarded as a hematological factor for poor tumor response in LARC, and higher NLR also represents worse tumor regression grade.

Background

Colorectal cancer is a common malignant tumor of digestive tract, with high morbidity and mortality(1). Rectal cancer accounts for about a third of all colorectal cancers(2), of which 45-55% of patients are diagnosed with locally advanced rectal cancer (LARC) and receive neoadjuvant chemoradiotherapy (CRT) (3). After CRT, 50-60% of patients may have different degrees of tumor regression, and 10-30% of patients may have complete pathological response(4). For subjects with complete clinical response, conservative operation plan or watch-and-wait strategy is recommended(5). However, the remaining 50% non-pathological responders(6), who fail to reduce tumor stage and benefit from CRT, have to bear a heavy financial burden and serious adverse consequences, such as side effects of CRT and tumor progression(7). Therefore, it is necessary to find predictive indicators before surgery to evaluate the pathological response of neoadjuvant CRT, thereby improving clinical treatment. Because of the simplicity of blood test, it has good maneuverability for predicting the therapeutic effect of CRT.

Tumor-related inflammation has been proved to be a key determinant of disease progression and survival(8). According to Global Cancer Statistics, chronic inflammation can increase the risk of developing cancer, and is link to more than 15% of all cancer deaths(9). Local and systemic inflammatory response is an important prognostic factor for colorectal cancer patients(10). In recent years, several studies have paid more attention on systemic inflammatory response indicators for predicting the prognosis of rectal cancer

after CRT(11-13). In particular, neutrophil-lymphocyte-ratio (NLR), monocyte-lymphocyte-ratio (MLR) and platelet-lymphocyte-ratio (PLR) are considered as prognostic biomarkers for patients with rectal cancer(13-16). Some studies have suggested that pre-CRT NLR and PLR, or NLR alone are independently related to tumor response(17, 18). Ishikawa et al. have suggested that NLR after CRT is more meaningful than that before treatment(12). Whereas Shen et al. reveled no statistical significance between hematologic parameters and tumor response(19).

Herein, the purpose of this retrospective observational trail was to evaluate the relationship between pathologic tumor response and hematologic parameters before and after CRT in LARC patients via propensity score-matched method, thereby determining whether blood parameters are potential indicators for predicting the tumor pathological response in LARC patients.

Methods

Patients

Totally 205 LARC patients from January 2008 to December 2017 were enrolled in this study. Inclusion criteria: the distance to the anal verge was less than 15 cm, and adenocarcinoma was diagnosed by histology. LARC (cT3-4 and / or N+) was evaluated by pelvic high-resolution magnetic resonance imaging, intrarectal ultrasound and CT. All participants were managed with neoadjuvant CRT and total mesorectal excision surgery.

Preoperative chemoradiotherapy and surgery

All patients underwent long-term radiotherapy. The radiation field was the whole pelvis, including the tumor or tumor bed and its surrounding 2-5 cm, presacral lymph nodes and internal iliac lymph nodes. The radiation dose was a total of 45-50.4 Gy with 1.8-2.0 Gy per fractions. These patients received radiotherapy accompanied by oral administration of capecitabine 825 mg/m^2 twice a week for 5 weeks. After chemoradiotherapy, they were given 2 cycles of consolidation chemotherapy (oxaliplatin 85 mg/m^2 and capecitabine 1000 mg/m^2).

Curative surgery was performed 8-11 weeks after the end of chemoradiotherapy, including laparoscopic or open anterior resection (AR) and abdominal-perineal resection (APR) surgery. After surgery, the tumor node metastasis (TNM) staging and pathological tumor regression grading (pTRG) were obtained according to American Joint Committee on Cancer (AJCC) 8th edition TNM staging system(20) and TRG system proposed by Mandard et al.(21). Besides, all cases were classified into good response (GR) group (ypTNM0-1) and poor response (PR) group (ypTNM2-4) based on pathological TNM (pTNM) classification. The primary endpoint was to evaluate the relationship between hematologic indicators and pathological response.

Hematologic markers

Hematologic parameters were collected at baseline (pre-CRT) and before surgery (post-CRT). Hemoglobin concentration, white ball cellcount (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count, and albumin level were obtained by fully automatic hematology analyzer (Sysmex XE-2100). NLR, MLR and PLR were defined as the ratio of neutrophils, Monocyte and platelets to lymphocytes.

Statistical analysis

SPSS software (version 23.0, IBM, Armonk, NY, USA) and R (version 3.5) were used for statistical analysis. A propensity score-matched method was adopted via multivariable logistic regression model based on age, gender, body mass index (BMI), distance to the anal verge (DTAV), histologic grade, clinical stage, operation type, hemoglobin and albumin concentration. Paired of patients were derived using 1:1 nearest-neighbor within PS score of 0.03. This strategy produced 73 matched pairs in each group (Fig. 1).

Continuous variables were described as mean ± standard deviation for normally distributed variables and median (interquartile range) for abnormally distributed variables. Categorical variables were expressed as absolute numbers (percentage). A Student's t-test or Mann-Whitney U test for continuous variables and Chi-square or Fisher exact test for categorical variables were used to compare the difference between two groups. After matching, both Mcnemar test for categorical variables and pared-samples Wilcoxon rank-sum test for continuous variables were performed. The cutoff point for the continuous variables was determined by the receiver operating characteristic (ROC) curves. Conditional logistic regression was used to define the correlation between the main potential parameters and pathological response of tumors. A two-sides p-value <0.05 was considered statistically significant.

Results

Patient characteristics

There were 105 patients in GR group and 100 patients in PR group. As shown in Table 1, there was significant difference in histologic grade between two groups. After propensity score matching, 73 patients in each group were enrolled in the study, and the difference in histologic grade was eliminated, suggesting that the data were comparable. Besides, the higher pre-CRT and post-CRT carcinoembryonic antigen (CEA) levels were related to the poor tumor response (p=0.026 and 0.002, respectively).

Table 1 Clinic characteristics of patients

Variables	All patients			Matched patients		
	GR group (n=105)	PR group (n=100)	*P*	GR group (n=73)	PR group (n=73)	*P*
Gender, n (%)			0.436			0.473
Male	66(62.9)	69(69.0)		46(63.0)	51(69.9)	
Female	39(37.1)	31(31.8)		27(37.0)	22(30.1)	
Age (years), n (%)			1.000			0.728
≥60	45(42.9)	43(43.0)		31(42.5)	34(46.6)	
<60	60(57.1)	57(57.0)		42(57.5)	39(53.4)	
BMI (kg/m^2)	22.10±3.70	22.10±3.53	0.800	22.10±3.70	22.10±1.94	0.554
DTAV (cm), n (%)			0.192			0.838
≥6	25(23.8)	33(33.0)		24(32.9)	26(35.6)	
<6	80(76.2)	67(67.0)		49(67.1)	47(64.4)	
Pre-CRT CEA (ng/ml), n (%)			0.022			0.026
≥5	33(31.4)	48(48.0)		20(27.4)	34(46.6)	
<5	72(68.6)	52(52.0)		53(72.6)	39(53.4)	
Post-CRT CEA (ng/ml), n (%)			0.005			0.002
≥5	12(11.4)	28(28.0)		6(8.2)	21(28.8)	
<5	93(88.6)	72(72.0)		67(91.8)	52(71.2)	
Histologic grade, n (%)			0.001			1.000
Low	1(0.9)	13(13.0)		1(1.4)	1(1.4)	
High	104(99.1)	87(87.0)		72(98.6)	72(98.6)	
Clinical stage, n (%)			0.345			1.000
II	12(11.4)	17(17.0)		12(16.4)	13(17.8)	
III	93(88.6)	83(83.0)		61(83.6)	60(82.2)	
Operation type, n (%)			0.196			1.000
AR	92(87.6)	80(80.0)		60(82.2)	61(83.6)	
APR	13(12.4)	20(20.0)		13(17.8)	12(16.4)	

GR: good response; PR: poor response; BMI: Body Mass Index; DTAV: Distance to the anal verge; CRT: chemoradiotherapy; CEA: Carcinoembryonic antigen; AR: Anterior resection; APR: Abdominal-perineal resection.

Hematological characteristics

Before CRT, there were significant differences in lymphocyte count, NLR, PLR and MLR between GR and PR groups (p=0.006, 0.002, 0.008 and 0.043, respectively). After adjusting with propensity score matching, the NLR and PLR in GR group were notably lower than those in PR group (p=0.014 and 0.025, respectively). No significant difference in lymphocyte count and MLR was noticed between the two groups (Table 2). Moreover, after CRT, there was no statistically significant difference in all hematological characteristics between two groups before and after propensity score matching (Table 3).

Table 2 Hematological characteristics before CRT

Variables	All patients			Matched patients		
	GR group (n=105)	PR group (n=100)	*p*	GR group (n=73)	PR group (n=73)	*P*
Hemoglobin (g/L)	145.00±21.00	138.50±29.25	0.056	140.00±21.00	141.00±23.00	0.574
WBC ($\times10^9$/L)	5.38±2.34	5.66±2.24	0.284	5.35±1.36	5.66±1.94	0.393
Neutrophil ($\times10^9$/L)	3.28±1.63	3.42±1.88	0.265	3.24±1.53	3.41±1.85	0.433
Lymphocyte ($\times10^9$/L)	1.58±0.80	1.27±0.81	0.006	1.58±0.68	1.43±0.87	0.149
Monocyte ($\times10^9$/L)	0.40±0.22	0.39±0.19	0.484	0.40±0.21	0.38±0.18	0.331
Platelet ($\times10^9$/L)	236.00±97.00	227.00±109.00	0.373	236.00±94.00	225.00±113.00	0.367
Albumin (g/L)	42.80±4.40	42.00±5.08	0.161	42.20±4.60	42.70±5.50	0.962
NLR	2.20±1.01	2.41±1.97	0.002	2.20±0.75	2.26±1.46	0.014
PLR	146.22±75.08	174.22±115.83	0.008	141.77±73.00	159.48±118.41	0.025
MLR	0.27±0.15	0.31±0.23	0.043	0.26±0.14	0.25±0.23	0.357

CRT: chemoradiotherapy; GR: good response; PR: poor response; WBC: White blood cell; NLR: neutrophil-lymphocyte-ratio; MLR: monocyte-lymphocyte-ratio; PLR: platelet-lymphocyte-ratio.

Table 3 Hematological characteristics after CRT

Variables	All patients			Matched patients		
	GR group (n=105)	PR group (n=100)	*P*	GR group (n=73)	PR group (n=73)	*P*
Hemoglobin (g/L)	139.00±19.00	134.00±20.00	0.487	138.00±21.00	134.00±19.00	0.482
WBC ($\times10^9$/L)	3.68±1.90	4.20±2.39	0.076	3.68±1.72	4.18±2.46	0.113
Neutrophil ($\times10^9$/L)	2.20±1.47	2.77±2.01	0.232	2.22±1.38	2.74±2.07	0.275
Lymphocyte ($\times10^9$/L)	0.76±0.46	0.79±0.56	0.198	0.72±0.43	0.75±0.55	0.666
Monocyte ($\times10^9$/L)	0.40±0.22	0.44±0.27	0.611	0.38±0.22	0.46±0.25	0.093
Platelet ($\times10^9$/L)	179.00±77.00	183.50±71.25	0.226	181.00±64.00	184.00±55.00	0.678
Albumin (g/L)	42.30±4.80	42.10±4.05	1.000	42.50±4.80	42.30±4.30	0.760
NLR	3.17±2.32	3.02±3.12	0.835	3.18±2.42	3.49±2.82	0.577
PLR	234.41±154.82	216.50±156.02	0.480	250.00±175.50	229.49±159.58	0.802
MLR	0.53±0.37	0.51±0.43	0.578	0.53±0.35	0.63±0.40	0.097

CRT: chemoradiotherapy; GR: good response; PR: poor response; WBC: White blood cell; NLR: neutrophil-lymphocyte-ratio; MLR: monocyte-lymphocyte-ratio; PLR: platelet-lymphocyte-ratio.

Predictive factors for tumor response

After analyzing the ROC curves of pre-CRT NLR, and pre-CRT PLR (Fig. 2), the cutoff values of pre-CRT NLR and pre-CRT PLR were 3.10 and 198.7, respectively (Table 4), and all patients were divided into two groups based on cutoff values. Factors with significant differences between the two groups were analyzed using a multivariate analysis model (Table 5). The results suggested that post-CRT CEA and pre-CRT NLR were the

predictors of tumor response (p=0.019 and 0.005, respectively), while pre-CRT PLR was not related with tumor response (p=0.472).

Table 4 Predictive value of prognostic factors

	AUC	95%CI	sensitivity	specificity
pre-CRT NLR	0.580	0.486-0.674	30.1	94.5
pre-CRT PLR	0.578	0.485-0.671	34.2	82.2

AUC: area under curve; CI: confidence interval; CRT: chemoradiotherapy; NLR: neutrophil-lymphocyte-ratio; PLR: platelet-lymphocyte-ratio.

Table 5 Multivariate analysis of tumor response

Variables	OR	95% CI	*P*
Post-CRT CEA (≥5 vs <5)	1.839	1.107-3.055	0.019
Pre-CRT NLR (≥3.10 vs <3.10)	2.047	1.241-3.377	0.005
Pre-CRT PLR (≥198.7 vs <198.7)	1.356	0.591-3.115	0.472

OR: odds ratio; CI: confidence interval; CRT: chemoradiotherapy; CEA: Carcinoembryonic antigen; NLR: neutrophil-lymphocyte-ratio; PLR: platelet-lymphocyte-ratio.

The association between the pre-CRT NLR and the TRG

According to the cutoff value, pre-CRT NLR was stratified into low NLR group and high NLR group. The relationship between pre-CRT NLR and TRG was analyzed and we found that 44.2% of patients had a poor TRG (TRG2-4) in low NLR group and 69.2% in high NLR group (Fig. 3), and this difference was statistically significant (p=0.036).

Discussion

The immune response of patients has important predictive significance not only in clinical prognosis, but also in the effects of radiotherapy and chemotherapy(22). Through the interaction of systemic and local inflammatory responses, the degree of leukocyte infiltration in tumor varies; besides, each leukocyte subtype, such as neutrophils, lymphocytes, NK cells, dendritic cells, participates in the formation of tumor microenvironment and is closely related to the invasion and metastasis of cancer(9). Therefore, the

assessment of the degree of inflammation in cancer can be used as a biomarker for clinical prognosis and treatment response. The analysis of circulating leukocyte subsets has become the most convenient method, especially for the analysis of NLR, PLR and MLR. Numerous studies have confirmed that they link to the prognosis of different cancers such as gastric cancer, ovarian cancer and colorectal cancer (15, 16, 23-25). NLR, PLR and MLR are known to be predictors of pathological response in LARC patients. Kim et al. suggested that NLR<2.0 and PLR<133.4 before CRT were associated with better tumor response(26). Kim et al. claimed that patients with baseline NLR>3 had poor tumor response(17), while Krauthamer et al. revealed that NLR<5 before CRT was related to better tumor response(18). In this study, hematologic parameters including NLR, PLR and MLR before and after CRT in LARC patients were analyzed to find the predictors of pathological tumor response, and we also adjusted selection bias by using propensity score-matched method. The initial univariate analysis of all patients showed that NLR, PLR and MLR were statistically significant between two group before CRT, but MLR was not statistically significant after matching. After multivariate analysis, NLR was the only significant predictor, suggesting that NLR>3.1 was associated with poor tumor response, with an odds ratio of 2.047, which was similar to the results of Kim. At the same time, TRG was poor in patients with NLR>3.1. Overall, pre-CRT NLR may be a potential marker for predicting the tumor pathological response in LARC patients.

Due to the cytotoxic effects of radiotherapy and chemotherapy, necrotic tumor cells increase antigen recognition, and this process changes the local and systemic inflammatory response(27). Therefore, it is possible to predict tumor response by NLR, PLR and MLR after CRT. Caputo and Ishikawa have suggested that NLR > 3.80 and 3.85 after CRT are predictors of poor tumor response(12, 28). However, no relationship between hematological factors and tumor response after CRT was observed in our study, which may be related to the uncontrolled factors that affect the systemic inflammatory response in the case enrollment phase. In addition, 6 cases had abnormally elevated neutrophils due to radiotherapy complications, and 9 cases received granulocyte colony stimulating factor treatment during radiotherapy. Moreover, hidden infections might also be potential causes for the differences in the results of this study.

There are some limitations in this study. This is a retrospective study without controlling the factors that affect the systemic inflammatory response. Secondly, after propensity matching, the sample size shrinks leads to insufficient evidence strength. Thus, prospective studies with a larger sample size are required for further confirmation in the future.

Conclusion

The increased NLR before CRT can be used as a hematological factor for poor tumor response, and higher NLR also represents worse TRG. It can be used as a simple tool in the clinical management of patients with LARC to help make a better treatment plan and ultimately improve the prognosis.

Abbreviations

LARC: Locally advanced rectal cancer

CRT: Chemoradiotherapy

NLR: Neutrophil-lymphocyte-ratio

MLR: Monocyte-lymphocyte-ratio

PLR: Platelet-lymphocyte-ratio

AR: Anterior resection

APR: Abdominal-perineal resection

TNM: Tumor node metastasis

pTRG: Pathological tumor regression grading

AJCC: American Joint Committee on Cancer

GR: Good response

PR: Poor response

pTNM: pathological tumor node metastasis

pre-CRT: Hematologic parameters collected at baseline

post-CRT: Hematologic parameters collected before surgery

WBC: White ball cellcount

BMI: Body mass index

DTAV: Distance to the anal verge

ROC: Receiver operating characteristic

CEA: Carcinoembryonic antigen

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University, and all subjects agreed to participate in our study with written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XN conceived and designed the study, and wrote the manuscript; LWL provided administrative support and collected patient clinicopathological data, and is corresponding author; HFC and YG performed analysis and interpretation of all data; WZQ and ZYF critically read the manuscript; ZJJ, ZRZ and YJY revised the paper. All authors approved the final version of the article to be published.

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Figures

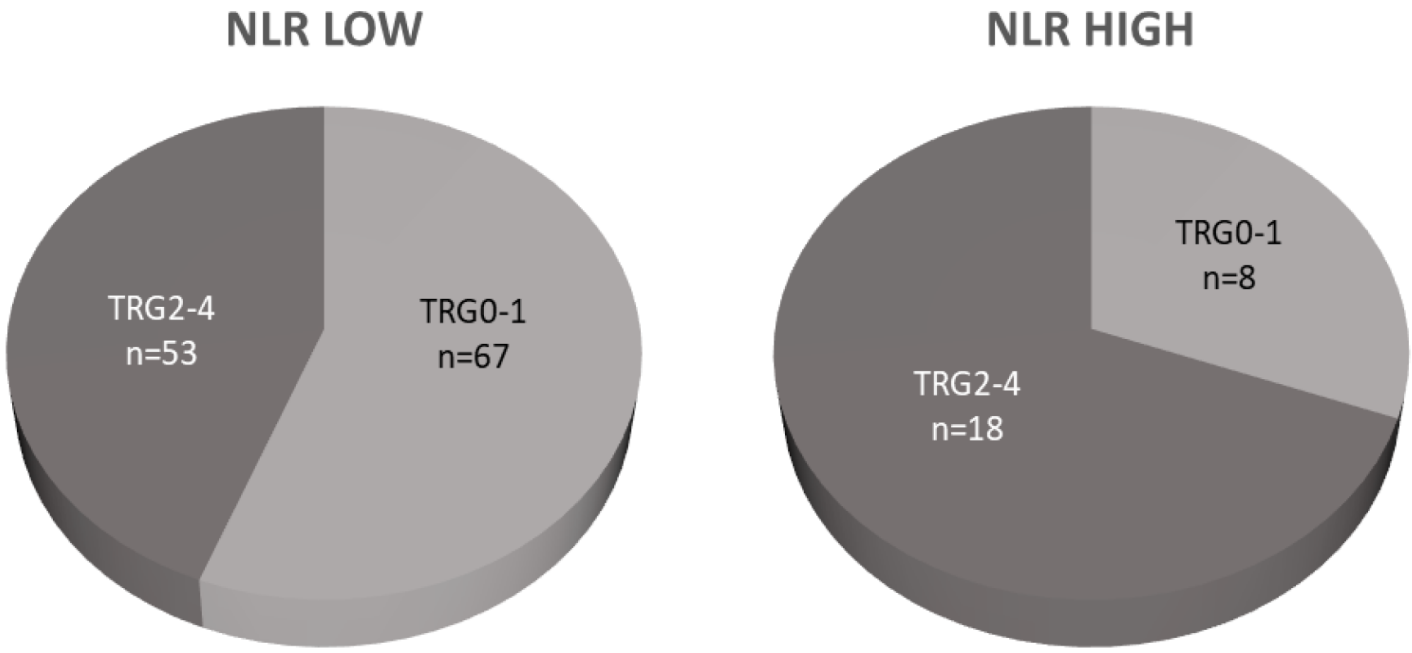

Figure 1

Pie charts of distributions according to the tumor regression grade in low NLR and high NLR group.

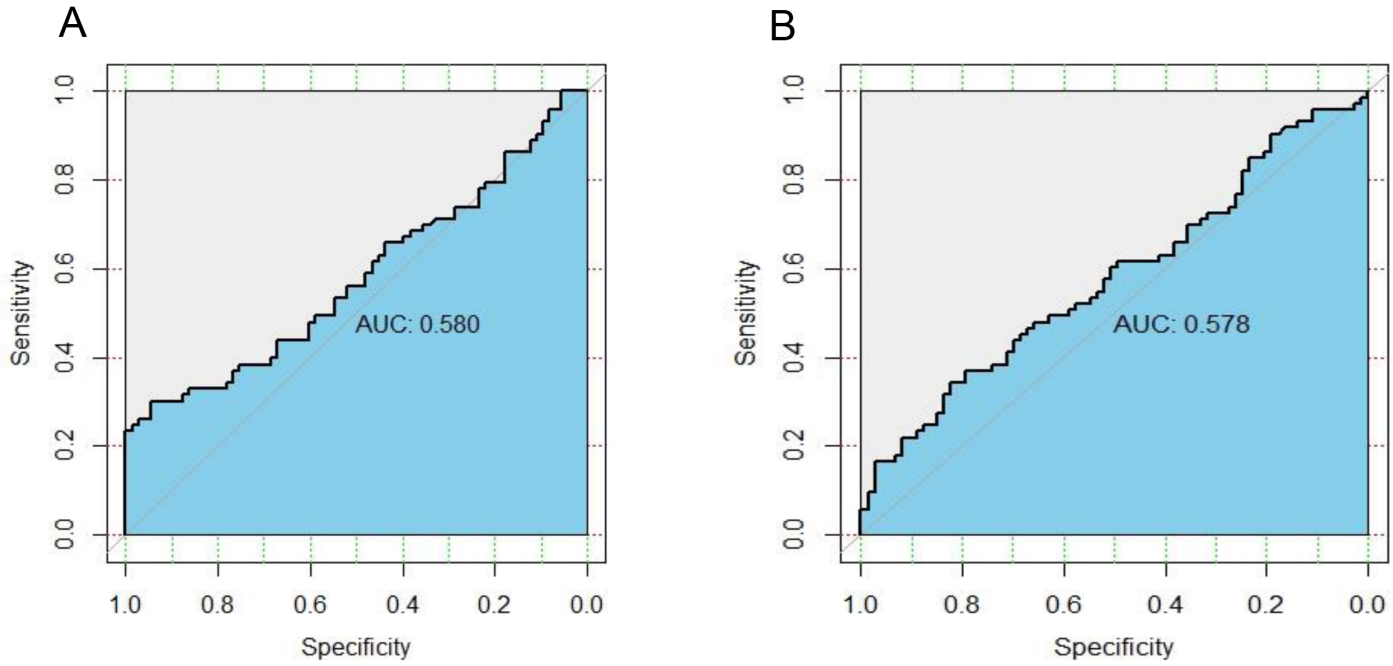

Figure 2

Receiver operating characteristic curves of (A) pre-chemoradiotherapy neutrophil-lymphocyte-ratio and (B) pre-chemoradiotherapy platelet-lymphocyte-ratio in predicting the tumor response.

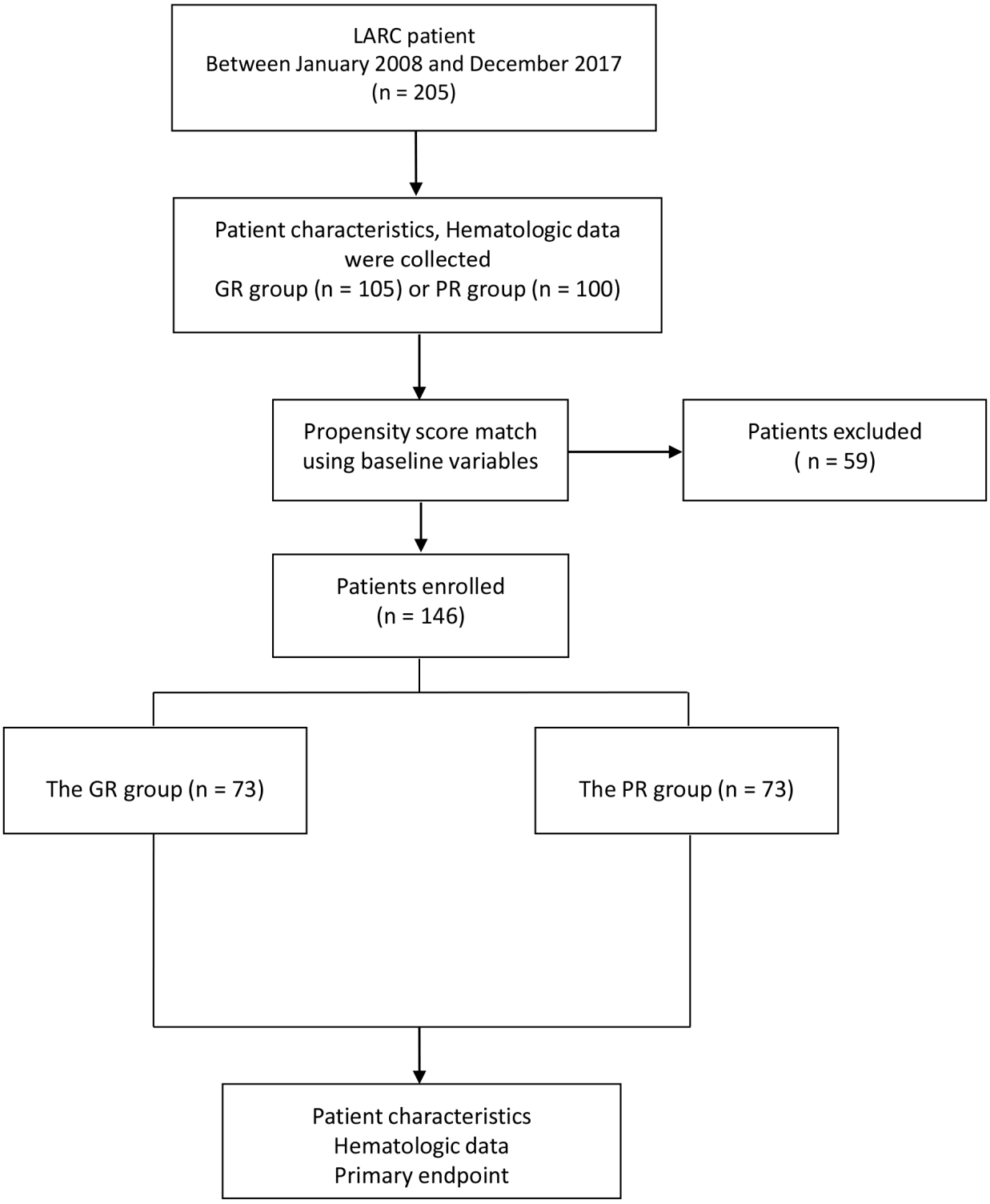

Figure 3

Flow chart of locally advanced rectal cancer patients.