

Prognostic Implications of the Peripheral PLR and NLR in Predicting pCR after NACT in Breast Cancer Patients

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Abstract

Background: Inflammatory response is extremely important in tumor progression, and it is very difficult to identify prognostic indicators for neoadjuvant therapy in breast cancer patients. The aim of this study was to mine the potential prognostic significance of the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in breast cancer patients receiving anthracycline- or taxane-based neoadjuvant chemotherapy (NACT).

Methods: Sixty-seven women diagnosed with breast cancer who received neoadjuvant therapy were enrolled in the study and then underwent surgeries. Before starting NACT, the PLR and NLR were calculated. The optimal cutoff value was calculated using receiver operating characteristic curve analyses, and the ROC curve analysis indicated that 106.3 and 2.464 were the best cutoff values for the PLR and NLR, respectively. The optimal cutoff values for the NLR and PLR were used to divide patients into low and high NLR groups and low and high PLR groups. Independent prognostic biomarkers and value the of PLR and NLR were assessed with univariate and multivariate logistic regression models. The connection between the NLR/PLR and pathological complete response (pCR), together with other clinical/pathological factors, was evaluated by Fisher's exact test or Pearson's χ^2 as appropriate.

Results: Logistic regression model analyses revealed that patients with a high PLR correlated remarkably with better pCR than those with a low PLR. The results indicated that by using the cutoff value of 106.3, PLR had prognostic significance. However, there was no significant difference in NLR if analyzed separately. However, by combining PLR and NLR, the NLR^{high} and PLR^{high} subgroups achieved a significantly higher rate of pCR than the NLR^{low}/PLR^{low} subgroup (OR 0.153, 95% CI 0.068-0.876, $p=0.008$). Therefore, the combination of NLR^{high}/PLR^{high} was an independent prognostic factor different from common factors, such as PLR, Ki-67, and chemotherapy regimen.

Conclusions: The PLR may serve as a potential marker of the efficacy of neoadjuvant therapy in breast cancer, enabling oncologists to intervene earlier. Peripheral blood NLR and PLR can reflect the immune status of patients. High levels of both of them may indicate immune activation status and predict the pCR rate of NACT treatment in breast cancer patients.

Introduction

Breast cancer is currently the highest-ranking cancer in the world in terms of morbidity and mortality among women^[1]. Currently, early-stage breast cancer generally has no symptoms and has a good prognosis, but many patients are locally advanced when they are diagnosed, and locally advanced tumor patients generally have a poor prognosis. Therefore, new biomarkers are urgently needed for the early diagnosis and detection of breast cancer to benefit more breast cancer patients.

Currently, neoadjuvant chemotherapy (NACT) is an effective measure for breast cancer treatment^[2], and it is increasingly used in locally advanced breast cancer. The advantages of NACT include that it can

reduce pathologic stage and increase potential breast conservation therapy, as well as its upfront treatment of micrometastatic cancer. In recent years, neotype chemotherapeutics have emerged significantly, and anthracycline- or taxane-based chemotherapy regimens are commonly used in clinical practice. It is urgent to find more precise biomarkers to obtain better survival outcomes for breast cancer patients.

The relationship between inflammation and cancer is the seventh hallmark of cancer and plays a significant role in the development of cancer^[3]. The relationship between them might represent a potential new method for cancer therapy. Many studies have reported that neutrophils (N), lymphocytes, white blood cells, and monocytes, as well as the lymphocyte-to-monocyte ratio (LMR), PLR and NLR, might be important biomarkers influencing carcinogenesis or tumor metastasis. In recent years, the relationship between breast cancer response to therapy and its immune microenvironment has become increasingly clear, and many studies are being conducted to verify the status of the peripheral immune system in breast cancer, especially the response to NACT^[4]. In summary, a lower parameter means reduced immune and inflammatory system activation, leading to worse or better results^[5, 6]. However, the response of these immune/inflammatory biomarkers in combination with other factors, such as PLR, molecular subtypes, chemotherapy regimen, grading, and Ki-67, to NACT has not been analyzed.

We enrolled 67 breast cancer patients who received NACT in our study. The purpose of this study was to evaluate the prognostic significance of the NLR and PLR in breast cancer patients who received anthracycline- or taxane-based neoadjuvant chemotherapy regimens. We researched whether the basal PLR and/or NLR can play a role in predicting pCR in neoadjuvant chemotherapy for breast cancer to distinguish them from other clinical factors.

Materials And Methods

Patients Selection

This study was reviewed and approved by the Second Affiliated Hospital of Zhejiang University School of Medicine. Sixty-seven patients with breast cancer were retrospectively identified using outpatient and inpatient databases between 2014 and 2019. The following eligibility criteria were used to select the study population: (1) biopsy-proven breast cancer, (2) baseline and follow-up complete blood counts (CBCs), including neutrophils and lymphocytes, performed at Second Affiliated Hospital and thus accessible through the electronic patient record (EPR), and (3) treatment with neoadjuvant chemotherapy. Patients who were participating in clinical trials or whose baseline data were not included in the EPR were excluded.

Treatment Protocols

Taxane and anthracycline are the most common NACT regimens for breast cancer. Other regimens include EC (epirubicin and cyclophosphamide), taxanes, or combinations with platinum vinorelbine or doxorubicin. HER2-positive patients were administered neoadjuvant trastuzumab. Surgical procedures

include breast-conserving surgery (BCS), mastectomy, sentinel lymph node biopsy or axillary lymph node dissection, as clinically demonstrated. Tumor staging was defined according to the 8th edition of the American Joint Committee Cancer Staging Manual. The project was approved by the local institutional review board. This study was conducted in accordance with the Declaration of Helsinki. All the participants provided informed consents. This study obeys the REMARK guidelines^[7].

Pathological assessments

All breast tumor specimens were sent for immunohistochemistry (IHC). Tumor cells with nuclear ER or PR receptor staining > 10% were defined as positive^[8]. Ki-67 was set at a cutoff point of 14% to distinguish luminal A and B^[9]. HER-2 positivity was confirmed by the ASCO/CaP guidelines or positive HER-2 gene amplification by FISH^[10]. The specimens were then classified as the following molecular subtypes: luminal A, luminal B/HER2-negative, luminal B/HER2-positive, triple-negative or HER2-enriched^[9]. The nuclear grade was assessed according to the Nottingham grading system^[11].

Peripheral Venous Blood Sample and data collection

Peripheral venous blood samples were routinely obtained and measured within 1 week before NACT. The cells were analyzed by an XE-2100 hematology analyzer (Sysmex, Kobe, Japan). All patient data included the clinical and pathological features, the type of treatment administered and related outcomes.

Follow-Up

For each 3-month interval, all outpatient and inpatient patients were routinely followed up during the first 2 years after surgery and then at 6-month intervals until death. Follow-up assessments included physical examination, laboratory tests, ultrasonication, multislice computed tomography, and other examinations. Pathologic complete response (pCR) was defined as the absence of invasive disease in the nodes and breast (ypT0/is ypN0) and was determined by reviewing pathology reports; ductal carcinoma-in situ was allowed^[12].

Statistical Analysis

Statistical analyses were performed using SPSS (version 25.0). The optimal cutoff values for the PLR and NLR were calculated using receiver operating characteristic (ROC) curve analyses. The area under the curve (AUC) was used to assess the predictive value. The ratio closest to the point with maximum sensitivity and specificity was defined as the optimal cutoff value. The independent prognostic factors and prognostic value of the PLR and NLR were assessed by univariate and multivariate logistic regression models. Odds ratios (ORs) were reported with the corresponding 95% confidence intervals (95% CIs). The relationships between the NLR/PLR and pCR, along with other clinicopathological characteristics, were evaluated by Pearson's χ^2 or Fisher's exact test as appropriate. A two-tailed $P < 0.05$ was considered a statistically significant difference.

Results

Patient and tumor baseline characteristics

We identified 75 patients diagnosed with breast cancer who were treated with consecutive NACT. In the end, 67 patients who had pretreatment CBC were included in the study. The baseline characteristics are listed in Table 1. The median age at first diagnosis was 51 years (range 27–81). The majority of cases were in tumor stage G2 at diagnosis (62.7%), and the main histology was invasive ductal carcinoma (92.5%). The patients showed 11.9% Luminal A molecular subtype, 19.4% Luminal B/HER2-negative, 19.4% Luminal B/HER2-positive, 17.9% triple-negative and 31.3% HER2-enriched. Only 9.0% of tumors were well-differentiated (G1), and 86.6% of patients expressed a Ki-67 proliferation index ($\geq 14\%$).

Relationship between NLR/PLR and baseline characteristics

The NLR cutoff point according to the ROC curve analysis was 2.464 (Fig. 1: ROC curve of PLR and NLR predict PCR). This point allowed the identification of the following two categories: NLR low (≤ 2.464), 45 patients (67.2%), and NLR high (> 2.464), 22 patients (32.8%). Similarly, the ROC curve for the PLR deduced a cutoff value of 106.3, and the following two categories of patients were identified (Fig. 1): 19 patients (28.4%) in the PLR^{low} (≤ 106.3) group and 48 patients (71.6%) in the PLR^{high} (> 106.3) group. The above data is shown in Table I. Following univariate analysis, Ki-67 $\geq 14\%$ patients showed higher probability to be NLR^{high}, while Ki-67 $\geq 14\%$ patients showed a higher tendency to be NLR^{low} ($p \leq 0.05$). Interestingly, patients in the luminal B/HER2 + molecular subtype subgroup were more inclined to be PLR^{high} ($p = 0.028$). No other baseline characteristics were significantly associated with either the PLR or NLR.

Table 1 Association of baseline characteristics to NLR or PLR.

Variable	N(%) n=67	NLR			PLR		
		Low(%) n=45	High(%) n=22	P value*	Low(%) n=19	High(%) n=48	P value*
Age (years)				0.516			0.610
≤50	25 (37.3)	18(72.0)	7(28.0)		8 (32.6)	17(68.0)	
>50	42 (62.7)	27(64.3)	15(35.7)		11 (26.2)	31(73.8)	
Histologic type				0.624			0.169
Ductal	62 (92.5)	41(66.1)	21(33.9)		16 (25.8)	46(74.2)	
Lobular	1 (1.5)	1(100.0)	0(0.0)		1 (100.0)	19(0.0)	
Others	4 (6.0)	3(75.0)	1(25.0)		2 (50.0)	19(50.0)	
Grade				0.087			0.269
G1	6 (9.0)	6(100.0)	0(0.0)		3 (50.0)	3(50.0)	
G2	42(62.7)	29(69.0)	13(31.0)		12 (28.6)	30(71.4)	
G3	15 (22.4)	8(53.3)	7(46.7)		4 (26.7)	11(73.3)	
Unknown ^a	4 (6.0)	2(50.0)	2(50.0)		0 (0.0)	4(100.0)	
Ki-67				0.034*			0.179
<14%	7 (10.4)	2(28.6)	5(71.4)		4 (57.1)	3(42.9)	
≥14%	60 (89.6)	43(71.7)	17(28.3)		15 (25.0)	45(75.0)	
Hormone Receptor(HR)				0.545			0.846
Positive	34 (50.7)	24(70.6)	10(29.4)		9 (27.3)	24(72.7)	
Negative	33 (49.3)	21(63.6)	12(36.4)		10 (29.4)	24(70.6)	
Molecular Subtype				0.633			0.028*
Luminal A	8 (11.9)	5 (62.5)	3(37.5)		1 (12.5)	7(87.5)	
Luminal B/HER2-	13 (19.4)	11 (84.6)	2(15.4)		8(61.5)	5(38.56)	

Luminal B/HER2 ₊	13 (19.4)	8 (61.5)	5(38.5)	1(7.7)	12(92.3)
HER2 enriched	21 (31.3)	13 (61.9)	8(38.1)	6(28.6)	16(71.4)
Triple Negative	12 (17.9)	8 (66.7)	4(33.3)	3(25.0)	9(75.0)

* Significant values are indicated in bold.

a Unknown not included in the analysis.

Association of the PLR/NLR and pCR in patients with breast cancer

For breast cancer with NLR and PLR, the pCR for patients with a high PLR was 19 and that of patients with a low PLR was 1, while the pCR for patients with a high and low NLR was 10. The results indicated that patients with a high NLR ($p = 0.580$) and high PLR ($p = 0.007$) had a higher pCR ratio than those with a low NLR and low PLR (Table 2).

Table 2 Association of patient/tumor characteristics to pCR in univariate analysis.

Variable	n(%) n=67	pCR(%) n=20	Odds ratio	95% CI	p value*
Age (years)					
≤50	25 (37.3)	4 (16.0)	1.000		
>50	42 (62.7)	16 (38.1)	0.481	0.099-1.187	0.083
Histologic type					
Lobular	1 (1.5)	0 (0.0)	No		
Others	3 (6.0)	1 (33.3)	1.000	No	No
Ductal	63 (94.0)	19 (30.2)	1.020	0.140-14.609	1.000
Grade					
Unknown	4 (6.0)	2 (50)	1.000		
G1	6 (9.0)	2 (33.3)	2.000	0.150-26.734	0.600
G2	42 (62.7)	11 (26.2)	3.200	0.398-25.733	0.274
G3	15 (22.4)	5 (33.3)	2.000	0.214-18.687	0.543
Ki-67					
<14%	7 (10.4)	1 (14.3)	1.000		
≥14%	60 (89.6)	19 (31.7)	0.392	0.040-3.200	0.665
Hormone Receptor(HR)					
Negative	33 (49.3)	14 (42.4)	1.000		
Positive	34 (50.7)	6 (17.6)	1.789	1.179-11.178	0.021
HER2					
Negative	33 (49.3)	5 (15.2)	1.000		
Positive	34 (50.7)	15 (44.1)	0.426	0.073-0.756	0.012
Molecular Subtype					
Triple Negative	12 (17.9)	4 (33.3)	1.000		
Luminal A	8 (11.9)	0 (0.0)	No	No	No
Luminal B/HER2-	13 (19.4)	0 (0.0)	No	No	No
Luminal B/HER2+	13 (19.4)	5 (38.5)	0.800	0.155-4.123	0.790
HER2 enriched	21 (31.3)	11 (52.4)	0.550	0.126-2.403	0.427

Chemotherapy regimen					
Chemio+Trastuzumab	28(41.8)	12(42.9)	1.000		
Various	12(17.9)	1(8.3)	0.140	0.038-3.518	0.382
Antracycline and Taxane	25 (37.3)	5 (20.0)	1.364	1.016-2.247	0.038
Unknown ^a	2(3.0)	2 (100)			
NLR					
High	22 (32.8)	10 (45.5)	1.000		
Low	45 (67.2)	10(22.2)	0.676	0.118-1.056	0.580
PLR					
High	48 (71.6)	19 (37.5)	1.000		
Low	19 (28.4)	1(10.5)	1.540	1.203-1.970	0.007
NLR/PLR					
High/High	19 (28.4)	9 (47.4)	1.000		
Low/High	30 (44.8)	9 (30.0)	2.100	0.638-6.916	0.222
High/Low	4 (6.0)	0 (0.0)	No	No	No
Low/Low	14 (20.9)	2 (24.3)	11.700	1.265-108.200	0.030
Surgery					
Mastectomy	61 (91.0)	18 (29.5)	1.000		
Breast-conserving surgery	6 (9.0)	2 (33.3)	1.175	0.201-7.114	1.000

* Significant values are indicated in bold.

^a Unknown not included in the analysis.

A thorough investigation into the efficiency of the PLR was analyzed by anthracycline or taxane regimens. We found that patients with a high PLR had a higher PCR ratio than those with a low PLR when receiving the Chemo + Trastuzumab regimen. With the Chemo + Trastuzumab regimen, the results showed

that the pCR for patients with a high PLR was 11 and that for patients with a low PLR was 1. Interestingly, it was easier to attain pCR in the NLR^{high}/PLR^{high} subgroup .

Relationship between pCR and baseline characteristics in patients with breast cancer

After NACT, 20 patients (29.9%) reached a pCR. High grade, Ki67 \geq 14%, HER-2 positivity, and HR negativity are classical poor prognostic factors for breast cancer, and the univariate analysis results related to pCR are shown in Table 2. In particular, the pCR probability was higher in the HR-negative subgroup compared to the HR-positive subgroup (OR 3.630, 95% CI 1.179–11.178, $p < 0.05$), and the Chemo + Trastuzumab subgroup had a higher pCR rate (OR 1.364, 95% CI 1.016–2.247, $p < 0.05$). Similarly, compared to the HER-2-negative subgroup, the HER-2-positive subgroup had a greater than 4-fold pCR rate (OR 4.263, 95% CI 0.073–0.756, $p < 0.05$). Consistently, luminal B/HER2+, HER-2-enriched or triple-negative subtypes had higher pCR rates than luminal A subtypes, but there was not a significant difference ($p = 0.069$). Neither the age nor the type of surgery subgroup was suitable to predict pCR in our study.

The combined NLR and PLR analysis makes sense for pCR. Consistently, we found that patients in the NLR^{high}/PLR^{high} subgroup had the highest rate of pCR (47.4%), and those in the NLR^{low}/PLR^{low} subgroup had the lowest rate (24.3%). NLR^{high}/PLR^{high} subgroup patients were two times as likely to reach pCR than NLR^{low}/PLR^{low} subgroup patients (OR 2.98, 95% CI 1.265–108.200, $p = 0.030$).

By multivariate analysis, only Ki-67, the chemotherapy regimen, PLR^{high} and NLR^{high}/PLR^{high} remained significant (Table 3). The Ki-67 \geq 14% subgroup had a five-fold higher pCR than patients in the Ki-67 $<$ 14% subgroup (OR 14.143, 95% CI 1.142–7.135, $p = 0.019$). Similarly, the NLR^{high} and PLR^{high} subgroup showed a more than 2-fold higher pCR rate than the NLR^{high} and PLR^{high} subgroup (OR 2.19, 95% CI 0.068–0.876, $p = 0.008$). Moreover, compared to the subgroup treated with the Chemo + Trastuzumab regimen, the pCR rate was higher (OR 1.719, 95% CI 1.020-10.889, $p = 0.005$). The same results were found for the PLR items (OR 2.150, 95% CI 1.972–5.639, $p = 0.008$).

Table 3
Association of patient/tumor characteristics to pCR in multivariate analysis.

Variable	OR	95% CI	P value*
TN/HER2 + vs Luminal HER2	1.930	0.038–98.076	0.058
Grading G2/G3 vs G1	0.552	0.003–21.505	0.263
Ki-67 \geq 14% vs Ki-67 $<$ 14	14.143	1.142–7.135	0.019
NLR ^{low} /PLR ^{low} vs NLR ^{high} and/or PLR ^{high}	0.153	0.068–0.876	0.008
PLR ^{low} vs PLR ^{high}	2.150	1.972–5.639	0.003
Hormone Receptor(HR) Negative vs Positive	0.885	0.046–16.926	0.935
HER2 Positive vs Negative	0.301	0.030–3.064	0.311
Chemio + Trastuzumab vs Chemio only	1.719	1.020-10.889	0.005
* Significant values are indicated in bold.			

Discussion

The latest studies focus on the contribution of the immune response to chemotherapy in tumors. There have been few studies on the NLR as a prognostic indicator of breast cancer, and the research conclusions are mixed. The NLR is a parameter reflecting the inflammatory response on behalf of the body, and the inflammatory response has an important relationship with tumor development and metastasis. Preoperative blood tests are convenient and easy to perform and are routine test items for breast cancer patients, with the characteristics of convenience and low price. Other inflammatory factors, such as C-reactive protein, play a significant role in the assessment of breast cancer and can also serve as independent predictors. Coffelt et al.^[13] found that neutrophils promoted tumor development and metastasis. There is a relationship between tumors and the immune response. It is certain that the NLR is related to the systemic immune response, mainly mediated by cytokines^[14]. Signal pathway transduction and activation of STAT3 as well as transcription factors such as NF- κ B, cytokines such as TNF- α and IL-6, and chemokines such as CCL2 and CXCL8 released from tumor cells and white blood cells are the main factors of tumor angiogenesis, tumor cell survival and proliferation. Neutrophils and NF- κ B can promote the survival and inhibit the apoptosis of neutrophils. Studies have confirmed that IL-1, TNF- α , IL-1 β and CXXL2 interact with neutrophils to promote tumor progression^[15, 16]. Changes in these factors lead to an increase in NLR.

Platelets play an important role in promoting tumor growth, angiogenesis and metastasis. Platelet granules contain abundant angiogenesis regulatory factors and growth factors, which are involved in the growth or angiogenesis of tumor cells. Activated platelets can also promote the proliferation of tumor

cells by releasing vesicles^[17]. The peripheral blood PLR index is a simple and feasible detection index, and current research results have confirmed that the PLR is closely related to the prognosis of liver cancer^[18], gastric cancer^[19], pancreatic cancer and other cancers^[20–22].

Our study provides proof that high PLR and NLR levels, tested before NACT in breast cancer patients, can predict the possibility of pCR. We retrospectively calculated the PLR and NLR from 67 breast cancer patients before starting NACT. We found that patients presented PLR > 106.3 and NLR > 2.464 according to ROC curve analysis. In contrast to previous studies, when analyzed separately, this study found that the PLR was an independent predictor of the pCR rate, which was not only closely related to the pCR rate of neoadjuvant chemotherapy for breast cancer but also combined with the NLR to predict the pCR rate. A higher pCR rate was observed in both the PLR^{high} and NLR^{high} subgroups (OR 2.98, 95% CI 1.265–108.200, p = 0.030). However, the NLR alone was not an independent predictor of the pCR rate, which may be closely related to the inflammatory microenvironment around the tumor. We analyzed and compared the relationship between pCR-related factors and the PLR in breast cancer neoadjuvant chemotherapy patients. Patients with a combination of NLR^{high} and PLR^{high} achieved a significantly higher pCR rate than the NLR^{low}/PLR^{low} subgroup (OR 2.19, 95% CI 0.068–0.876, p = 0.008), indicating that an immunogenic phenotype is a good predictor of chemotherapy response and that combined studies can better identify immunophenotypes in patients.

This study also found that Ki-67 \geq 14% patients showed a higher probability of pCR, which was related to the clinical finding that Ki-67 indicates nuclear proliferation, and patients with a higher probability had a worse prognosis. In terms of pathological types, ductal carcinoma had no direct relationship with pCR. The hormone receptor negative, HER-2 positive and chemo + trastuzumab chemotherapy regimen were associated with a higher probability of pCR, and there was no difference in age, molecular subtype, grade or surgery type.

Other interesting findings have been gained from this study. The PLR and NLR had no connection with clinical/pathological characteristics, except Ki-67. For example, the Ki-67 \geq 14% subgroup had a significantly higher rate of NLR^{high}, Ki-67 \geq 14% patients had a significantly higher NLR^{low} rate, and for the molecular subtype, the luminal B/HER2 + subgroup showed a higher PLR^{high} proportion.

In summary, preoperative PLR, as a convenient, practical, simple and inexpensive hematological inflammatory indicator, plays an important role in predicting the pCR rate of neoadjuvant chemotherapy for breast cancer and can provide help for patients to select appropriate treatment plans before surgery.

This study has some limitations. There is still a lack of further data on the correlation between detailed tumor staging and PLR on the NACT pCR rate; thus, relevant studies need to be further improved. There are several subtypes in the data that have zero numbers, leading them to not be analyzed statistically. In the future, more samples and larger studies are needed to further confirm the relationship between the PLR and the efficacy of neoadjuvant therapy for breast cancer. In this study, preoperative coarse needle aspiration was used to confirm the diagnosis of breast cancer patients, and interference of infection,

bleeding, immune diseases and other factors were excluded as much as possible. However, our study showed that the NLR alone was not an independent predictor of the pCR rate, which may be caused by the selective bias of patients enrolled in both groups and retrospective studies. In the future, we will perform more complementary studies to improve these limitations.

Declarations

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Authors' contributions

XJ, KW, XS, and JH conceived and designed this study. XJ, KW, and XS helped with data collection and summary. XJ, KW, XS, and JH were responsible for data analysis and interpretation. All authors made contributions to manuscript writing. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request

Ethics approval and consent to participate

Ethics approval and consent to participate The study was approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine.

Consent for publication Not applicable

Not applicable

Competing interests

The authors declare that they have no competing interests

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Figures

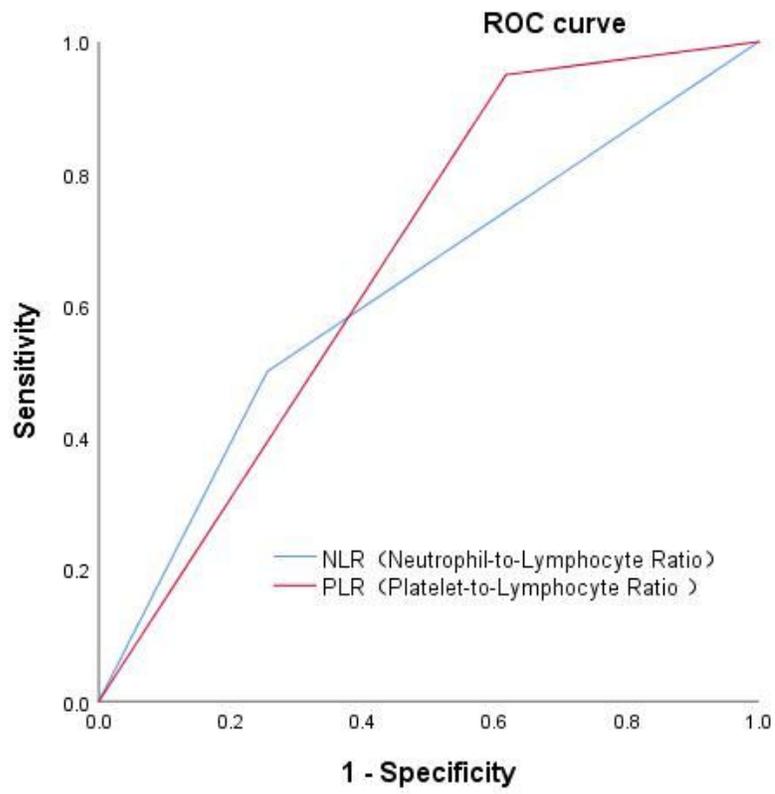


Figure 1

ROC curve of PLR and NLR predict PCR