


The correlational study about neutrophil-to-lymphocyte ratio and exercise tolerance of chronic obstructive pulmonary disease patients

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Abstract

To study the relationship between neutrophil to lymphocyte ratio (NLR) and exercise tolerance of patients with chronic obstructive pulmonary disease (COPD).

235 patients with COPD were selected as the study subjects. Complete blood count, C reactive protein (CRP), pulmonary function tests, the 6-minute walk distance (6MWD), Modified Medical Respiratory Council, the COPD assessment test, and clinical COPD questionnaire were tested. Heart rate, oxygen saturation, and Borg scale were tested before or after 6MWD test.

By the median of NLR, the subjects were divided into 2 groups, NLR ≥ 4.5 group and NLR < 4.5 group. The white blood cell count (WBC), CRP and deoxygenation saturation in the NLR ≥ 4.5 group were higher than those in the NLR < 4.5 group, while the age, body mass index (BMI), 6MWD, and heart rate variation were lower than those in the NLR < 4.5 group. CRP, WBC, and deoxygenation saturation had positive effects on NLR, BMI, 6MWD, and heart rate variation had negative effects on NLR. The Pearson correlation analysis showed NLR was positively correlated with WBC, CRP, BMI index, 6MWD, and deoxygenation saturation, while it was negatively correlated with BMI and heart rate variation.

NLR might associate with exercise tolerance and cardiorespiratory reserve of COPD patients, and could be used as an indicator of muscle function in COPD patients.

Abbreviations: 6MWD = 6-minute walk distance, AECOPD = acute exacerbations of COPD, BMI = body mass index, CAT = COPD assessment test, CCQ = clinical COPD questionnaire, COPD = chronic obstructive pulmonary disease, CRP = C reactive protein, MMRC = Modified Medical Respiratory Council, NLR = neutrophil to lymphocyte ratio, WBC = white blood cell count.

Keywords: chronic obstructive pulmonary disease, exercise tolerance, neutrophil to lymphocyte ratio

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequently occurring disease that seriously threatens human health. It is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.^[1] According to the latest epidemiological survey of COPD in China, the prevalence of COPD among Chinese over 40 years old increased from 8.2% in 2008 to 13.7% in 2015.^[2] As a systemic disease, COPD can also cause systemic or extrapulmonary adverse reactions, among which muscle dysfunction is one of the common systemic manifestations of COPD.^[3] Various mechanisms can lead to muscle dysfunction in COPD patients, such as abnormal deoxygenated type I muscle fiber and mitochondrial contents in the muscle system, imbalance of oxidative stress to promote muscle protein degradation, hypoxemia and hypercapnia also impair the oxidative ability of muscles and affect the synthesis and degradation of contractile proteins.^[4-6] Systemic inflammatory response in COPD patients is closely related to exercise tolerance, which can produce a series of responses through the expression of transcription factors and apoptosis mechanism.^[7,8] This systemic adverse reaction seriously affects the quality of life of COPD patients, clinically manifested as decreased exercise ability and/or physical activity, increasing the morbidity and mortality of COPD. Therefore, accurate assessment and rational intervention of patients' muscle

functional status is one of the important aspects of COPD management.

The ratio of neutrophils to lymphocytes (NLR), which is calculated from complete blood count with differential, is an inexpensive widely available marker of inflammation, which can reflect the immune status and systemic chronic inflammation. As a marker of systemic inflammation, the NLR is an independent predictor of multiple malignancies and is associated with recurrence and death of severe nutritional status in a variety of chronic diseases, such as cardiovascular diseases, sepsis, and infectious conditions.^[9–11] More and more studies have found that NLR is also involved in the development of COPD. Lee et al reported that the NLR in the acute episode of COPD patients was higher than that in the stable period and the healthy control group, while the NLR significantly decreased in the recovery period of patients with acute exacerbation.^[11] Taylan et al also found that the NLR of COPD patients gradually increased with the aggravation of the disease, which indicated that NLR could be used as an early predictor of the acute episode of COPD patients.^[12] These studies confirm that NLR has important diagnostic value in assessing the severity and acute exacerbations of COPD. However, the association between the NLR and exercise tolerance in COPD patients has not been well studied. The purpose of this study was to explore the relationship between NLR and exercise tolerance, and to analyze the value of NLR in the diagnosis of muscle function in COPD patients.

2. Materials and methods

2.1. Subjects

The research objects were 235 cases of patients with COPD diagnosed by the Department of Respiration at our hospital from July 2018 to July 2019. The diagnosis of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease documents.^[13] Written informed consent was obtained from all patients. This study was approved by the local institutional review board of our hospital in accordance with the tenets of the Helsinki Declaration (No. 2018022). The inclusion criteria were as following:

- (1) patient with symptoms of chronic cough and expectoration shortness of breath and (or) risk factors (eg, smoking), the ratio of post-bronchodilator forced expiratory volume in 1 second to forced vital capacity was <0.7 according to the Global Initiative for Chronic Obstructive Lung Disease guidelines^[14];
- (2) COPD patients with acute exacerbations were well after treatment and follow-up of at least 1 month in a stable condition;
- (3) asthma overlap syndrome patients, due to they have the clinical characteristics of COPD and are one of the phenotypes of COPD.

The exclusion criteria were as following:

- (1) patients with pneumonia, pulmonary abscess, tuberculosis (clinical manifestations, radiographic manifestations of chest computed tomography or X-ray, tuberculosis antibody, and T-SPOT.TB test) bronchiectasis, bronchial asthma, interstitial lung disease, lung cancer, and other respiratory diseases;
- (2) patients unable to complete routine C-reactive protein (CRP) and/or the 6-minute walk distance (6MWD) test;
- (3) Patients with osteoarthritis, femoral head necrosis, and other disorders that affect 6MWD test.

2.2. Measurements

Gender, age, body mass index (BMI), smoking history, complications, medical treatment history, the number of acute exacerbations of COPD in the year before enrollment and the duration of disease were recorded. Blood routine and CRP detection were completed by the department of laboratory of our hospital.

All the enrolled patients were examined the pulmonary function in our hospital (Pulmonary Function Testing System; MODEL, chestac-33:8,800). The test was strictly carried out by professionals in Department of Respiratory in accordance with the operating guidelines for lung function,^[15] repeated 3 times each time and taken the maximum value. Each patient completed lung ventilation function detection and bronchial dilation test.

The 6MWD test was performed to evaluate the exercise tolerance of the enrolled patients according to the standards of the American Thoracic Society.^[16] The subjects were asked to walk back and forth as quickly as possible on a 30-meter long corridor for 6 minutes according to physical ability. The walking distance was measured, the environment was kept quiet and air circulation was maintained during walking, and blood pressure before and after walking was recorded. The test was conducted for 2 times, with an interval of half an hour. If the distance difference between the 2 times was less than 10%, the mean value was taken; if the condition was not met, the mean value was increased by 1 time. Before walking, the notes should be explained to the patient in detail. If chest pain, dizziness, intolerance, shortness of breath, and other obvious discomfort appear during walking, the test should be immediately terminated. Oxygen saturation and heart rate were measured before and at the end of 6MWD test, and the measured results were used as the base and final values, respectively, and Borg dyspnea score was completed after the results were recorded.

The degree of dyspnea was assessed using the Modified Medical Respiratory Council (MMRC) dyspnea scale. The MMRC score ranges from 0 to 4 and increases with the severity of dyspnea.^[17] The COPD assessment test (CAT) was used to evaluate the clinical symptoms of patients, it has 8 questions, each was divided into 0 to 5 points according to the severity, and the total score was the final score of CAT and increases with the severity of disease. The clinical COPD questionnaire (CCQ) was used to evaluate the symptom control of patients. There were 10 questions in the CCQ, and each question has a score range of 0 to 6. The total CCQ score was calculated by adding up the scores of the 10 questions and dividing by 10.

2.3. Statistical analysis

SPSS 23.0 statistical analysis software was adopted to conduct statistical analysis on the research data. The categorical variables were expressed by frequencies and percentages, and the continuous variables were expressed by means \pm standard deviation or median. The Kolmogorov–Smirnov test was used to determine the normal distribution of continuous variables. The 2-sample *t* test or Mann–Whitney test were used to test the 2 sample continuous variables according to whether they conform to the normal distribution. The forced introduction regression method (Enter) in linear regression was used to analyze the regression of variable rows. The correlation between the 2 variables was analyzed by Pearson correlation. Statistical significance was determined to exist at $P < .05$ with a 2-tailed test.

Table 1
Baseline characteristics of patients.

Characteristics	Total patients (n=235)	NLR <4.5 group (n ₁ =117)	NLR ≥4.5 group (n ₂ =118)	P-value
Age (yr)	65.64 ± 6.37	66.57 ± 5.99	64.72 ± 6.62	.03
Gender (n, female/male)	172/63	85/32	87/31	.85
BMI (kg/m ²)	22.24 ± 4.39	22.95 ± 4.54	21.54 ± 4.15	.01
Disease duration (d)	3502.04 ± 4136.59	3452.79 ± 3912.72	3350.88 ± 4363.42	.86
Acute exacerbations of COPD (times)	1.30 ± 1.17	1.36 ± 1.21	1.24 ± 1.14	.42
CRP (mg/L)	5.60 ± 3.61	4.78 ± 3.67	6.41 ± 3.37	.00
WBC (×10 ⁹ /L)	8.06 ± 3.47	7.20 ± 3.50	8.92 ± 3.23	.00
RBC (×10 ¹² /L)	4.47 ± 0.62	4.49 ± 0.63	4.45 ± 0.62	.65
Hg (g/L)	134.83 ± 18.79	136.69 ± 18.58	133.00 ± 18.89	.13
Platelets (×10 ⁹ /L)	241.63 ± 80.35	234.58 ± 73.63	248.63 ± 86.24	.18
Eosinophil (×10 ⁹ /L)	0.18 ± 0.69	0.25 ± 0.97	0.11 ± 0.17	.15
FVC (L)	1.90 ± 0.48	1.90 ± 0.51	1.19 ± 0.46	.88
FEV1 (L)	1.09 ± 0.46	1.10 ± 0.47	1.09 ± 0.45	.81
FEV1, predicted (L)	2.28 ± 0.45	2.31 ± 0.48	2.25 ± 0.41	.28
FVC, predicted (L)	3.09 ± 0.69	3.14 ± 0.74	3.03 ± 0.64	.39
CAT score	29.32 ± 4.43	28.85 ± 4.57	29.79 ± 4.26	.10
CCQ score	3.54 ± 0.52	3.49 ± 0.52	3.60 ± 0.52	.11
MMRC dyspnea score	3.30 ± 1.04	3.23 ± 1.10	3.32 ± 0.97	.54
6MWD (meter)	395.04 ± 85.90	425.43 ± 88.36	364.91 ± 71.96	.00
Diabetes mellitus (n)	22	12	10	.64
History of medication (n)				.11
Irregular use	89	38	51	
LAMA	42	28	14	
ICS+LABA	71	36	35	
ICS+LABA+LAMA	17	9	8	
Theophylline	16	6	10	
History of heart disease (n)				.02
Coronary heart disease	104	47	57	
Cardiac insufficiency	32	12	20	
Others	8	2	6	

6MWD = 6-minute walk distance, BMI = body mass index, CAT = COPD assessment test, CCQ = COPD questionnaire, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ICS = inhaled corticosteroids, LABA = long-acting beta-agonist, LAMA = long-acting muscarinic antagonist, MMRC = Modified Medical Respiratory Council, NLR = neutrophil-to-lymphocyte ratio, RBC = red blood cell, WBC = white blood cell.

3. Results

In this study, a total of 235 patients with the median NLR value 4.5 were included. According to the study method of Nam et al,^[18] the patients were divided into NLR ≥4.5 group and NLR <4.5 group. The baseline characteristics of the enrolled patients were shown in Table 1. The mean NLR value were 6.67 ± 1.37 and 2.93 ± 1.00 in NLR ≥4.5 group and NLR <4.5 group, respectively. There were significant difference in terms of age, BMI, CRP, cardiac complications, white blood cell (WBC) count, and 6MWD between 2 groups (all $P < .05$), while other baseline characteristics had no significant difference (all $P > .05$).

Multivariate Linear Regression Analysis showed that both CRP ($\beta = 0.12$, 95% confidence interval [CI]: 0.05–0.19, $t = 3.52$, $P < .01$) and WBC ($\beta = 0.15$, 95% CI: 0.08–0.22, $t = 4.27$, $P < .01$) had positive effects on NLR, BMI ($\beta = 0.09$, 95% CI: 0.14–0.03, $t = 3.07$, $P < .01$) and 6MWD ($\beta = 0.01$, 95% CI: 0.01–0.00, $t = 5.63$, $P < .01$) had effects on NLR, however, there was no significant relationship between age, history of heart disease (coronary heart disease, cardiac insufficiency, others) and NLR, as shown in Table 2. After Pearson correlation analysis, it was found that NLR was positively correlated with WBC ($r = 0.26$, $P < .01$) and CRP ($r = 0.30$, $P < .01$), and negatively correlated with BMI ($r = -0.20$, $P < .01$) and 6MWD ($r = -0.39$, $P < .01$), as shown in Table 3 and Figure 1.

To analyze the relationship between NLR and patients' motor function, the deoxygenation saturation, heart rate variability, and Borg index of NLR ≥4.5 group and NLR <4.5 group were further analyzed. The deoxygenation saturation of NLR ≥4.5 group was statistical higher than that of NLR <4.5 group ($t = 5.71$, $P < .01$). The heart rate variability of NLR <4.5 group was statistical higher than that of NLR ≥4.5 group ($t = 2.32$, $P < .05$). There was no significant difference in term of Borg between the

Table 2
Correlation between NLR and Clinical Parameters in COPD.

Variables	Coefficient	T	P-value	95% CI
Age (yr)	−0.01	−0.73	.47	−0.05
BMI (kg/m ²)	−0.09	3.07	<.001	−0.14
WBC (×10 ⁹ /L)	0.15	4.27	<.001	0.08
CRP (mg/L)	0.12	3.52	<.001	0.05
6MWD (meter)	−0.01	−5.63	<.001	−0.01
No heart disease	1.05	2.93	<.001	0.34
Coronary heart disease	−0.07	−0.18	.86	−0.86
Cardiac insufficiency	−1.01	1.53	.13	2.32
Other Disease	−1.05	−1.36	.19	−2.57

6MWD = 6-minute walk distance, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, WBC = white blood cell.

Table 3
Correlation between NLR and clinical parameters in COPD.

Parameters	R	P
WBC ($\times 10^9/L$)	0.26	<.001
CRP (mg/L)	0.30	<.001
6MWD (meter)	-0.39	<.001
BMI (kg/m^2)	-0.20	<.001

6MWD = 6-minute walk distance, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, NLR = neutrophil-to-lymphocyte ratio, WBC = white blood cell.

2groups ($t=2.23$, $P=.823$, Table 4). After linear regression analysis, it was found that heart rate variability ($\beta = -0.07$, 95% CI: -0.12 to 0.02 , $t=2.89$, $P < .05$) had a negative effect on NLR, while deoxygenation saturation ($\beta = 0.79$, 95% CI: $0.56-1.03$, $t=6.75$, $P < .01$) had positive effect on NLR (Table 5). After Pearson correlation analysis, it was found that NLR was positively correlated with deoxygenation saturation ($r=0.41$, $P < .01$) and negatively correlated with heart rate variability ($r=-0.19$, $P < .01$, Table 5 and Fig. 2)

Table 4
The correlation parameters of the 6MWD were compared between the 2 groups.

	NLR <4.5 group	NLR ≥ 4.5 group	Statistics	P-value
Deoxygenation saturation (%)	6.67 ± 1.03	7.46 ± 1.06	5.71	<.001
Heart rate variability	21.02 ± 6.02	19.36 ± 4.89	2.32	.02
Borg index	4.75 ± 1.87	4.81 ± 1.76	0.22	.82

6MWD = 6-minute walk distance, NLR = neutrophil-to-lymphocyte ratio.

4. Discussion

The decrease of muscle strength and endurance caused by muscle dysfunction is one of the important clinical manifestations of COPD, which makes the patient’s exercise tolerance gradually reduce and seriously affects the quality of life of patients. At present, the cause of muscle dysfunction in COPD patients is still unclear, but it has been proved to be related to inflammatory oxidative stress and muscle maladjustment in COPD patients.^[19]

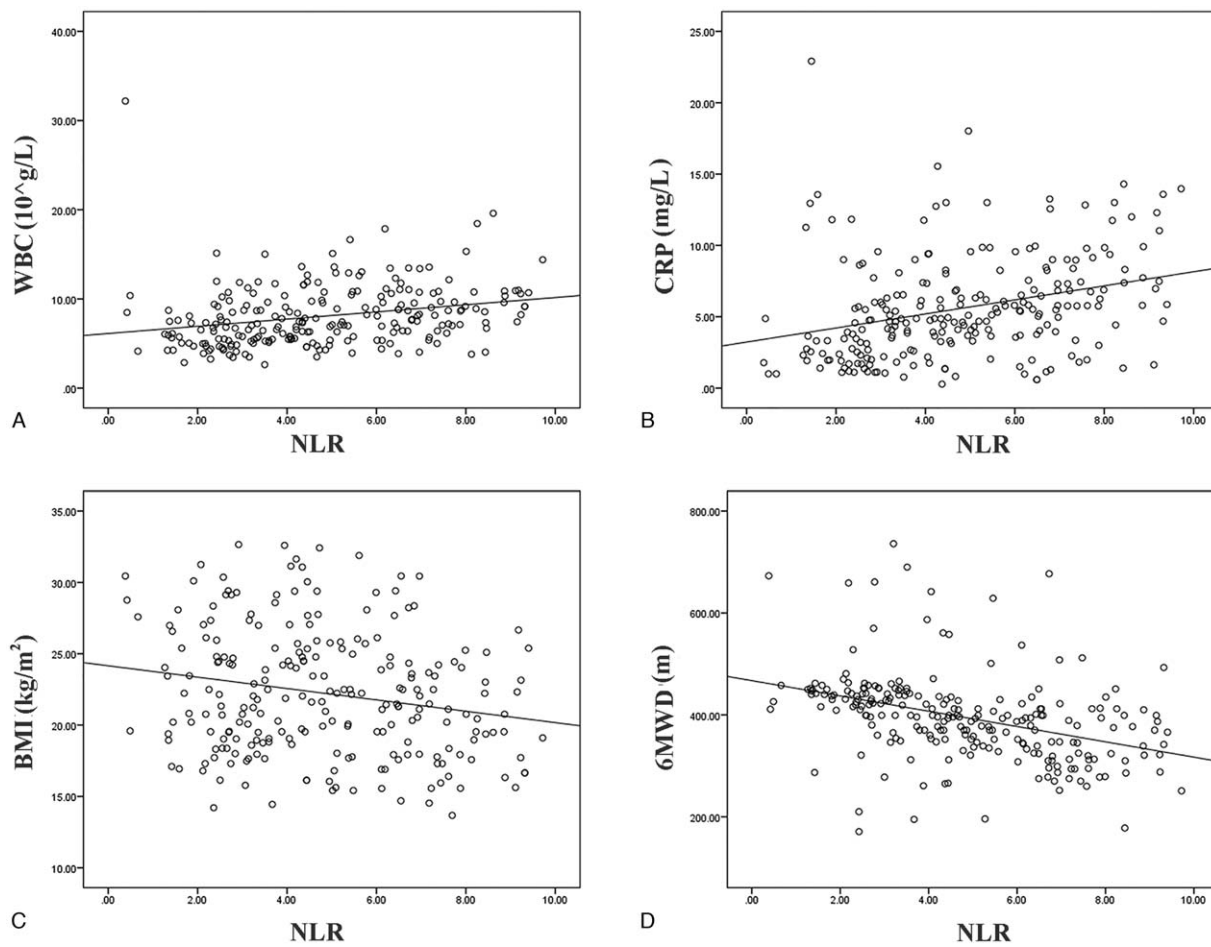


Figure 1. The correlation analysis of various parameters between NLR and COPD patients. (A) Correlation between NLR and white blood cells (WBC) ($r=0.26$, $P < .01$) (B) Correlation between NLR and C reactive protein (CRP) ($r=0.30$, $P < .01$) (C) Correlation between NLR and body mass index (BMI) ($r=-0.20$, $P < .01$) (D) Correlation between NLR and 6-min walk distance (6MWD) ($r=-0.39$, $P < .01$). COPD = chronic obstructive pulmonary disease, NLR = neutrophil-to-lymphocyte ratio.

Table 5
Analysis of experimental parameters of 6MWD and NLR in COPD patients.

Variables	Linear regression				Pearson correlation	
	Coefficient	T	P-value	95% CI	R	P-value
Deoxygenation saturation (%)	0.79	6.75	<.001	0.56	0.41	<.001
Heart rate variability	-0.07	2.89	.04	-0.11	-0.19	<.001
Borg index	-0.06	0.87	.39	-0.08	0.07	.27

6MWD=6-minute walk distance, COPD=chronic obstructive pulmonary disease, NLR=neutrophil-to-lymphocyte ratio.

Therefore, inflammatory markers may be one of the ideal markers for monitoring COPD muscle dysfunction. The results of this study suggested that NLR is related to exercise ability and cardiopulmonary reserve in COPD patients, and might be a candidate marker for monitoring muscle dysfunction in COPD patients.

Although the pathogenesis of COPD has not been fully elucidated, the role of persistent inflammatory response in the development of COPD has been widely recognized. Blood routine includes leukocyte subsets, which are easily acquired inflammatory indicators in clinical practice and are considered as markers of many inflammatory diseases, but there are many interfering factors, such as congestion and anemia. While, NLR can reflect the body's non-specific inflammatory response and the state of the immune system, with good stability, and has been widely studied in the prediction of COPD disease progression and clinical outcomes. NLR is an effective predictor of re-exacerbation of COPD and is associated with rehospitalization and mortality.^[20,21] The eosinophil phenotype is one of the important phenotypes of COPD. A comparison between the eosinophil phenotype and the non-eosinophil phenotype in acute exacerbations of COPD (AECOPD) patients revealed that NLR was related to the severity of the acute phase of COPD and may be used to guide the treatment of AECOPD.^[22] Yao et al found that the mortality sensitivity and specificity of hospitalized AECOPD patients predicted by NLR were 81.08% and 69.17%, respectively, which indicated NLR could be as a predictor of in-hospital mortality in AECOPD patients.^[23] Furutated et al

found that, after analyzing 141 COPD patients, NLR was positively correlated with MMRC score, emphysema degree and BODE index, and negatively correlated with forced expiratory volume in 1 second%, 6MWT, BMI, and nutritional status.^[24] However, this study showed that compared with patients with NLR <4.5, patients with NLR ≥4.5 showed a decrease in BMI, 6MWD, while there was no difference in MMRC, CAT score and lung function. The reason for this result may be related to the included population experimental design and the heterogeneity of disease. CRP and WBC are indicators of systemic inflammation. The results suggested that there was a correlation between NLR and CRP and WBC, which was consistent with previous studies.^[25-27] However, the above study did not further study the cardiopulmonary function reserve of COPD patients.

The 6MWD test is a kind of submaximal exercise, which can comprehensively reflect the overall response of the heart, lungs, and muscle system of the whole body, can reflect the functional status and mortality of COPD patients well, and can reflect the ability of daily life of COPD patients.^[28,29] As mentioned above, NLR is correlated with 6MWD, and our further study found that NLR is associated with heart rate variation and deoxygenation saturation in 6MWD test. Heart rate variation and deoxygenation saturation reflect cardiopulmonary reserve function. Abnormal heart rate after 6MWD test was related to morbidity and mortality of a variety of diseases, and can predict the acute exacerbation of COPD.^[30] Decreased oxygen saturation during exercise was associated with severe air flow obstruction in the lungs.^[31] Therefore, it was speculated that NLR may also have an

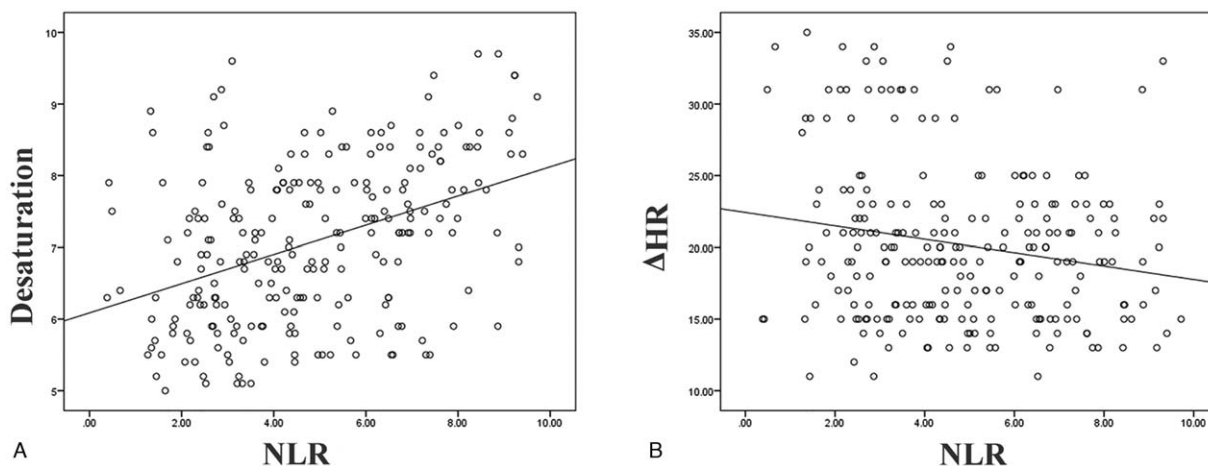


Figure 2. The correlation analysis between NLR and parameters of 6MWD test. (A) Correlation between NLR and deoxygenation saturation ($r=0.41, P<.01$) (B) Correlation between NLR and heart rate variability (ΔHR) ($r=-0.19, P<.01$). 6MWD=6-minute walk distance, NLR=neutrophil-to-lymphocyte ratio.

auxiliary diagnostic role in the functional status of COPD such as exercise capacity.

The NLR can be used to assess motor capacity and muscle function in COPD patients, and the mechanisms may be as follows. COPD is a chronic inflammatory disease characterized by neutrophils and macrophages, in which the persistent inflammation could lead to abnormal aggregation of WBC, lymphocytes, and neutrophils in peripheral blood. Lymphocytes play an important regulatory role in inflammatory factors of COPD and are involved in its progression.^[25,32,33] These inflammatory cells and factors can affect the regeneration ability of satellite cells, leading to abnormal proliferation of skeletal muscle, changes in muscle fiber type and muscle atrophy.^[34] However, in the process of COPD progression, patients often merged the diseases such as acute infection, metabolic disorders, whether and how to exclude this kind of patients in the application of NLR judgment muscle dysfunction, which will be study in further research in future.

5. Conclusion

In summary, this study provides evidence for NLR as a marker for monitoring COPD patients' exercise ability, which may become an important monitoring method for stable COPD rehabilitation treatment. However, this study was limited to a small sample size, and large-scale and high-quality studies, including the relationship between specific NLR range and muscle function, is needed to further determine.

Author contributions

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