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Original Article

Correlation between high sensitivity C reactive protein (Hs-CRP) and neutrophil-to-lymphocyte ratio (NLR) with functional capacity in post COVID-19 syndrome patients

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Abstract

Post coronavirus disease 2019 (COVID-19) syndrome is one of the causes of reduced functional capacity and work productivity, in particular for healthcare workers. The pathophysiology of the post COVID-19 syndrome is related to complex and multisystem inflammatory mechanisms, and cardiopulmonary exercise rehabilitation program is one of the efforts to improve the recovery process for patients with post COVID-19 syndrome. The aim of this study was to determine the correlation between the level of high sensitivity C-reactive protein (Hs-CRP) and neutrophil-to-lymphocyte ratio (NLR) with functional capacity (VO_{2max}) in individuals with post-COVID-19 syndrome who received moderate- and high-intensity supervised cardiopulmonary exercise. A prospective cohort study was conducted at the Integrated Cardiac Rehabilitation Center of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. The supervised cardiopulmonary exercise was conducted for six weeks according to the participant's baseline VO_{2max}. Spearman's and Pearson's correlation tests were used to assess the correlations. A total of 30 individuals (19 and 11 had moderate and high intensity exercise, respectively) were involved in this study. At moderate intensity exercise, the average Hs-CRP and NLR were 3.3 mg/L and 1.99, respectively; while at high intensity, the values were 3.8 mg/L and 1.79, respectively. No significant correlation between Hs-CRP level and functional capacity in both moderate-intensity and high intensity groups. In contrast, NLR was negatively correlated with functional capacity (r=-0.545, p=0.016) in moderate intensity exercise group. In conclusion, NLR value was negatively correlated with functional capacity in individuals with post-COVID-19 syndrome after receiving moderate intensity supervised cardiopulmonary exercise program. Therefore, moderate intensity of cardiopulmonary exercise maybe be used as a program to accelerate the recovery for those with post COVID-19 syndrome.

Keywords: Long COVID-19, cardiopulmonary exercise, functional capacity, Hs-CRP, NLR

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Introduction

The chronic symptomatic form of coronavirus disease 2019 (COVID-19) is known as post-COVID-19 syndrome or post-COVID-19 syndrome [1]. National Institute for Health and Care

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Excellence (NICE) of the United Kingdom defined post-COVID-19 syndrome as symptoms persisting for >12 weeks while long COVID-19 as ongoing symptoms of COVID-19 lasting for 4–12 weeks [2]. The symptoms of the post-COVID-19 syndrome represented organ damages that occurred during the acute phase of the illness. However, strong evidence was recently found that patients with mild or moderate acute symptoms of COVID-19 might still develop symptoms of unrelated to the organ dysfunctions that occurred during the acute phase [3].

Multisystem symptoms due to multiple organ injury in severe cases of COVID-19 mainly because the activation of the immune system indicated by increased the expression of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), and high acute phase reactants such as ferritin and C-reactive protein (CRP) that are triggering a cytokine storm [4]. The level of serum CRP significantly correlated with the post-COVID syndrome [5]. A study reported that serum CRP levels could help to determine the prognosis and to evaluate disease improvement of COVID-19 [6]. CRP specificity value was higher than other biological markers, such as procalcitonin, D-dimer and ferritin [6]. In contrast, another study found no association between CRP, white blood cell count, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR) or lactate dehydrogenase (LDH) levels with post-COVID fatigue [7].

Physical exercise has been proven to be beneficial in increasing functional capacity, the capability to perform aerobic work as defined by the maximal oxygen uptake (Vo_{2max}); and Vo_{2max} is the sum of cardiac output and arteriovenous oxygen difference at physical exhaustion [8]. Previous studies reported that there was an effect of a supervised cardiopulmonary rehabilitation program on increasing functional capacity in post-COVID-19 patients [9, 10]. Physical exercises increase the immune response in various inflammatory conditions characterized by increased leukocyte mobilization and increased systemic inflammatory mediators produced by immune cells and directly from active muscle tissue [11]. Routine moderate-intensity exercise had a favorable effects in reducing most of the inflammatory mediators, including CRP, TNF-α, and IL-6, and conversely increasing the production of anti-inflammatory cytokines [4, 12] where the increase in functional capacity was inversely proportional to the levels of inflammatory mediators [13].

The contrasting results of the association between exercise and CRP levels suggested uncertainty of the effectiveness of exercise to reduce CRP levels independently [14]. The result of the previous meta-analyses showed that there was no significant improvement in CRP after physical exercise in children and adults [15, 16]. Previous studies investigating the relationship between exercise and NLR showed that higher NLR was associated with lower functional capacity but some did not reach statistical significance [17, 18]. Studies evaluating the effect of exercise on high sensitivity CRP (Hs-CRP) level and NLR in individuals with post-COVID-19 syndrome are limited; therefore, studies assessing the relationship between functional capacity and inflammatory markers in post-COVID-19 syndrome are needed. The aim of this study was to determine the association between functional capacity with Hs-CRP and NLR in patients with post-COVID-19 syndrome. Moreover, this study is expected to disclose the evidence of prolonged inflammatory responses in post-COVID-19 syndrome and the benefit of exercise program to accelerate recovery in individuals with post-COVID-19 syndrome.

Methods

Study design and setting

A prospective cohort study was conducted at the Integrated Cardiac Rehabilitation Center at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. The study was conducted between May and October 2021. Clinical data, VO_{2max}, Hs-CRP and leucocyte levels were measured prior and six weeks after completing supervised cardiopulmonary exercise program. All individuals were medical professionals who had confirmed COVID-19 from January 2020 to March 2021. The time of completing the exercise programs were different for each participant as they started at a different time.

Study participants

The participants of the study were healthcare workers aged between 20–58 years who had COVID-19 infection previously, both hospitalized and non-hospitalized with mild and moderate symptoms and had been declared recovered and were able to perform daily activities without any assistance. However, all of them still experiencing residual symptoms >12 weeks after the onset of infection. The COVID-19 infection was confirmed by RT-PCR nasopharyngeal swab. The classification of mild and moderate symptoms was based on the Guidelines on the Diagnosis and Treatment of COVID-19 published by the National Health Commission of China [19]. The participants with a history of chronic obstructive pulmonary disease, asthma, heart disease (heart failure, coronary heart disease, heart valve disease, and uncontrolled rhythm abnormalities), kidney failure, malignancy, uncontrolled hypertension, post-stroke, and confirmed with COVID-19 more than once, were excluded. Additionally, those who could not complete all exercise programs were dropped from the study.

Study variables

Before the exercise program started, the age, sex, body mass index (BMI), blood pressure and heart rate, VO_{2max}, Hs-CRP, leucocyte and other routine blood tests were measured on the same day. The VO_{2max} of all participants representing functional capacity that was obtained from multiplying metabolic equivalent (MET) by 3.5 (1 MET is equal to 3.5 mL/kg/min); examined from stress test with WHO Bike protocol using Ergometer E-bike Basic device following the manufacturer's guideline (Ergoline GmbH, Bitz, Germany). The Hs-CRP was measured using high sensitivity immunoturbidimetry (Abbott, Illinois, USA) and leucocyte levels were measured using flowcytometry method using semiconductor laser (Sysmex XN550, Sysmex Europe, Norderstedt, Germany), at Prodia Laboratory, Banda Aceh, Indonesia. NLR was calculated from the ratio between neutrophil and lymphocyte from the leucocyte counts. After six weeks of weeks of exercise program, the VO_{2max}, Hs-CRP, and leukocyte level data were remeasured.

In addition, systolic and diastolic blood pressure, heart rate and routine blood test parameters (hemoglobin, hematocrit, mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and erythrocyte sedimentation rate (ESR) were also measured before and after the program.

Exercise program intervention

The supervised cardiopulmonary exercise was carried out for six weeks (12 times, twice a week) according to the participants' basic VO_{2max} measured at starting of the study and consisted of either moderate or high intensity exercise. If the participants could reach 3–5.9 METs, they received moderate intensity exercise, and if they could reach ≥6 METs, a high intensity exercise was provided. Moderate intensity was described as continuous aerobic type exercise with duration 30 min/day and prescribed as walking on a treadmill (G6485 Pioneer R2, BH Fitness, Pain Vasco, Spain) at a starting speed of 3 miles per hour (mph) with target 55–69% of maximum heart rate. While, high intensity was an interval high intensity aerobic type with the same duration and prescribed as jogging or running on a treadmill with a starting speed of 4.5 mph to reach the target 70–89% of maximum heart rate. The exercise prescription was based on American College of Sports Medicine definition of moderate and high intensity activities [20]. All the exercise programs were fully trained by certified personnel and monitored by a cardiologist at Cardiac Rehabilitation Gym Installation at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia.

Statistical analysis

Continuous variables with normal distribution were presented as mean (standard deviation (SD); non-normal variables were reported as median (minimum-maximal). Categorical variables were presented as frequency and percentage. Independent t-test or Mann Whitney were used to compare numeric data while Pearson χ^2 or Fisher's exact test were used to compare categoric data between moderate and high intensity of supervised cardiopulmonary exercise. To assess the correlations between Hs-CRP and leukocyte levels with functional capacity, Pearson correlation test or Spearman's rank correlation were used as appropriated based on the normality test using

the Shapiro–Wilk test analysis. The correlation coefficients (r values) were classified as very low (0–<0.2), low (<0.4), moderate (<0.6), high (<0.8) and very high correlation (0.8–1). A value of $p<0.05$ was considered significant. All analyses were conducted using SPSS version 23.0 (IBM SPSS, New York, United States).

Results

Individuals' characteristics between moderate and high intensity exercise

A total of 30 individuals (19 moderate and 11 high exercise intensity) were included in this study, with an average age of 40.11 and 33.09 years for moderate and high exercise intensity, respectively (**Table 1**). The moderate exercise group was dominated by the female (78.9%), while the high exercise group was dominated by the male (81.8%). There was a significant difference in functional capacity between the moderate and high intensity groups after supervised cardiopulmonary exercise ($p<0.001$) (**Table 1**). However, the assessment based on inflammatory markers (Hs-CRP and NLR) between groups after exercise showed no significant difference ($p>0.05$).

Table 1. Characteristics of the individuals who received moderate and high intensity of exercise, both pre-exercise and post-exercise

Characteristics	Cardiopulmonary exercise intensity		*p*-value
	Moderate (n=19)	High (n=11)	
Age (year), mean ± SD	40.11±8.89	33.09±6.37	0.030*
Sex, n (%)			0.002*
Male	4 (21.9)	9 (81.8)	
Female	15 (78.9)	2 (18.2)	
Body mass index (kg/m²), mean ± SD	27.58±4.62	25.26±3.24	0.156
Pre-intervention			
Systolic BP (mmHg), mean ± SD	114.11±10.41	122.45±18.55	0.124
Diastolic BP (mmHg), median (min-max)	80 (60–90)	80 (60–103)	0.805
Heart rate (beats per minute), median (min-max)	89 (72–120)	88 (64–104)	0.473
VO_{2max} (mL/kg/min), median (min-max)	17.5 (12.2–30.8)	26.25 (17.5–36.7)	0.002*
Hs-CRP (mg/L), median (min-max)	4.1 (2.3–10.3)	4 (2.2–10.2)	0.966
Neutrophil-leucocyte ratio, mean ± SD	1.93±0.47	1.74±0.54	0.336
Post-intervention			
Systolic BP (mmHg), mean ± SD	113.84±10.74	125.64±17.58	0.030*
Diastolic BP (mmHg), median (min-max)	70 (60–90)	80 (60–90)	0.160
Heart rate (beats per minute), mean ± SD	89.32±13.94	89.45±12.05	0.978
VO_{2max} (mL/kg/min), mean ± SD	21.97±3.81	30.38±5.65	<0.001**
Hs-CRP (mg/L), median (min-max)	3.3 (2.3–18.8)	3.8 (2.5–8.7)	0.846
Neutrophil-leucocyte ratio, median (min-max)	1.99 (0.97–2.37)	1.79 (1.1–2.4)	0.533

BP: blood pressure; SD: standard deviation
* Statistically significant at $p=0.05$
** Statistically significant at $p=0.001$

Characteristics of blood test parameters moderate and high intensity exercise

The pre-exercise and post-exercise routine blood test results for both moderate and high intensity exercise group are presented in **Table 2**. On pre-exercise, hemoglobin, hematocrit, erythrocytes, platelets, and leukocytes did not show any significant differences between the two groups. In contrast, hemoglobin content (MCH and MCHC) and cell variation (RDW) in red blood cells between groups had significant differences (all had $p<0.05$). The average neutrophil count had no different between moderate and high exercise groups ($p=0.161$) (**Table 2**).

Post-exercise routine blood test data showed higher hemoglobin levels in the high intensity group than in the moderate group, with a difference of 1.4 gr/dL ($p=0.031$) (**Table 2**). A similar difference was shown for hemoglobin content in cells (MCH and MCHC) between the two groups (both $p<0.05$). Although, the mean neutrophil count in the moderate exercise group was relatively higher compared to the high intensity group (a difference of 3.2%), this had no significant difference ($p=0.312$) (**Table 2**).

Table 2. Comparation of routine blood test parameters between individuals who received moderate and high intensity, both pre-exercise and post-exercise

Phase	Parameter	Supervised cardiopulmonary exercise		*p*-value
		Moderate (n = 19)	High (n = 11)	
Pre-exercise				
	Hemoglobin, mean ± SD	13.27±1.85	14.4±1.35	0.089
	Hematocrit, mean ± SD	40±5.06	42.15±3.42	0.222
	Erythrocyte, mean ± SD	4.83±0.52	5±0.48	0.407
	MCV, median (min-max)	84.3 (68.6–91.4)	85.4 (80.4–86.8)	0.780
	MCH, mean ± SD	27.45±2.56	28.8±0.71	0.041*
	MCHC, mean ± SD	33.14±1.03	34.14±0.74	0.009*
	RDW, median (min-max)	13.2 (11.7–19.9)	12.4 (11.6–13.3)	0.037*
	Thrombocyte, mean ± SD	299.42±48.43	277.36±48.58	0.240
	Leucocyte, mean ± SD	7.26±1.54	7.32±1.12	0.905
	Basophile, mean ± SD	0.45±0.24	0.43±0.22	0.812
	Eosinophile, median (min-max)	1.6 (0.6–7.2)	2.8 (1.1–15.5)	0.132
	Neutrophil, mean ± SD	58.86±5.78	55.07±8.65	0.161
	Lymphocyte, mean ± SD	31.56±4.84	33±5.78	0.469
	Monocyte, median (min-max)	6.2 (4.8–11)	6.8 (5.3–11.7)	0.426
	ESR, median (min-max)	18 (3–55)	5 (2–28)	0.029
Post-exercise				
	Hemoglobin, mean ± SD	13.2 (11.5–15.6)	14.6 (11.5–15.6)	0.031*
	Hematocrit, mean ± SD	40.2 (31.1–47.3)	42.8 (34.8–45.2)	0.067
	Erythrocyte, mean ± SD	4.67 (4.15–5.73)	5.2 (3.99–5.33)	0.189
	MCV, median (min-max)	82.62±6.8	84.36±2.36	0.320
	MCH, mean ± SD	27.24±2.67	28.7±0.82	0.037*
	MCHC, mean ± SD	32.94±1.07	34±0.93	0.011*
	RDW, median (min-max)	13 (11.7–18.8)	12.6 (11.5–13.5)	0.131
	Thrombocyte, mean ± SD	304 (266–409)	261 (239–350)	0.282
	Leucocyte, mean ± SD	6.87±1.65	7.68±7.5	0.226
	Basophile, mean ± SD	0.5±0.21	0.44±0.26	0.509
	Eosinophile, median (min-max)	2.52±1.51	3.41±1.67	0.144
	Neutrophil, mean ± SD	60 (44.7–64.7)	56.8 (45.7–64.4)	0.312
	Lymphocyte, mean ± SD	30 (26.4–45.9)	32.2 (26–41.6)	0.576
	Monocyte, median (min-max)	6.81±1.14	6.9±0.88	0.818
	ESR, median (min-max)	13 (3–50)	9 (3–20)	0.110

* Statistically significant at $p<0.05$

Correlation between high sensitivity C-reactive protein (Hs-CRP) and functional capacity

There was no significant correlation between Hs-CRP and functional capacity of those who received moderate intensity with $p=0.276$ (**Table 3**). Our data also indicated no significant correlation between Hs-CRP and functional capacity in high intensity group (**Table 3**).

Table 3. Correlation between sensitivity C-reactive protein (Hs-CRP) and functional capacity in individuals after moderate and high intensity exercise

Intensity	Variable	Median	Min - Max	*r*	p-value*
Moderate				-0.263	0.276
	VO_{2max}	21.0	15.7–28.0		
	Hs-CRP	3.3	2.3–18.8		
High				0.164	0.629
	VO_{2max}	29.7	19.25–38.5		
	Hs-CRP	3.8	2.5–8.7		

* Analyzed using Spearman's correlation test

Correlation between neutrophil-to-lymphocyte ratio (NLR) and functional capacity

Our data indicated that NLR was negatively correlated with functional capacity among individuals who received moderate exercise with moderate correlation ($r=-0.545$) (**Table 4**). However, there was no correlation between NLR and functional capacity among individuals who received high intensity exercise (**Table 4**).

Table 4. Correlation between neutrophil-to-lymphocyte ratio (NLR) and functional capacity in individuals after moderate and high intensity exercise

Intensity	Variable	Median	Min - Max	*r*	p-value
Moderate				-0.545	0.016 [a,*]
	VO_{2max}	21.0	15.7–28.0		
	NLR	1.9	0.97–2.3		
High, mean± SD					
	VO_{2max}	30.38±5.65	-	-0.143	0.676 [b]
	NLR	1.78±0.38	-		

[a] Analyzed using Spearman's correlation test
[b] Analyzed using Pearson correlation test
* Statistically significant at $p<0.05$

Discussion

NICE defines post-COVID-19 syndrome as symptoms persisting for >12 weeks [2] and it is estimated that the prevalence ranges from 3% to 11.7%, with a substantial impact on decreased quality of life, both social and professional, as well as disruption of daily activities [21]. The functional capacity assessment describes the ability to carry out daily activities that require aerobic metabolism. Combined activities involving the respiratory, cardiovascular, and skeletal muscle systems can determine one individual's functional capacity [8] and it is usually assessed using a treadmill machine or bicycle ergometer [22, 23].

From our study we found that the average Hs-CRP level were above normal value both on moderate and high intensity exercise groups before exercise program (4.1 and 4 mg/L). This was also reported in a previous study which found CRP levels that remained high in 120 patients three months after recovering from COVID-19 infection [25]. Hs-CRP levels were normal if <0.3 mg/dL and elevated Hs-CRP usually occurs in conditions of systemic inflammation [26].

Our data suggested that there was no significant correlation between Hs-CRP and functional capacity after having moderate and high intensity supervised cardiopulmonary training in patients with post-COVID-19 syndrome. This finding aligned with a previous meta-analysis, which found that exercise intensity did not reduce chronic inflammation levels [27]. The duration of exercise that the sample in this study participated in was six weeks, and Hs-CRP levels decreased but did not reach normal values. A previous study reported that the Hs-CRP level decreased below 0.3 mg/dL at 12 weeks after moderate exercise in 29 women with a mean age of 74.2 years [26].

This study found that the NLR values of moderate and high intensity groups before exercise were 1.93 and 1.74, respectively. NLR normality value as previously proposed (0.78–3.58) [28]. The average NLR value in patients with post-COVID-19 syndrome after moderate intensity supervised cardiopulmonary exercise was 1.83, and the average functional capacity was 21. The NLR value was negatively correlated with functional capacity with moderate correlation. A significant correlation between NLR and VO_{2max} was not found in subjects who underwent high-intensity supervised cardiopulmonary exercise.

The exercise intensity strongly affected the value of NLR and functional capacity [29, 30]. A previous study reported that moderate intensity aerobic exercise for two weeks increased the number of leucocytes count in COVID-19 patients with mild and moderate symptoms [31]. The reason is that aerobic exercise accelerates the recruitment of natural killers, T cells and B cells in the bloodstream. Natural killers proliferate more compared to T cells, leading to a decrease in the CD3+ T cells percentage and this facilitates the recruitment process of leucocyte and as the result increasing the number of leukocytes [32]. Another study reported that NLR value was within normal range but slightly higher at 30 min after high intensity exercise compared to pre-exercise in healthy volunteers [33]. Elevated cortisol levels on high intensity exercise was thought to be responsible on promoting a pro-neutrophil and anti-lymphocyte condition, inhibit mitogenesis, accelerate lymphocyte apoptosis resulting in lower lymphocyte count, as well as increasing the release of neutrophils to the bloodstream, leads to higher count of these cells at the end of exercise [11,33]. To the best of our knowledge, there was no study involving high intensity exercise on post COVID-19 patients.

The study had some limitations that must be taken into account. Firstly, it was performed on patients from a single health care center and the results may not be generalized to other populations or geographical areas. Furthermore, this study recruited a relatively small number of samples. A longer period of exercise program is potential to see the effect of duration on further reduction of inflammatory markers.

Conclusion

A negative correlation was observed between NLR and functional capacity in individuals with post-COVID-19 syndrome after undergoing moderate intensity supervised cardiopulmonary exercise. Although the average Hs-CRP level decreased after supervised cardiopulmonary exercise in both moderate and high intensity, the correlations between Hs-CRP and functional capacity in both groups were not significant.

Ethics approval

The study was approved by the Health Research Ethics Committee, Dr Zainoel Abidin Hospital, Banda Aceh, Indonesia (ref no 200/EA/FK-RSUDZA/2021).

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Competing interests

The authors declare no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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