ORIGINAL ARTICLE

Effects of Upper Arm and Breathing Exercise on Interleukin-6 in COVID-19 Patients

Amira Permatasari Tarigan[1*], Aditya Sri Listyoko[6], Pandiaman Pandia[1], Andika Pradana[1], Putri Chairani Eyanoer[2], Sudirman Parningotan Sinaga[3], Yeni Vera[4], Ruby Firdaus[1], Adini Arifah Ramadhani[5]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[2]Department of Preventive and Community Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[3]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[4]Department of Physiotherapy, STIKes Siti Hajar, Medan, Indonesia.
[5]Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia.
[6]Doctoral Student, Division of Respiratory Medicine and Rheumatology, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Tottori, Japan.

ARTICLE INFO

Article history:
Received 19 October 2023
Received in revised form
2 January 2024
Accepted 19 January 2024
Available online 30 January 2024

Keywords:
Breathing exercise,
Infectious disease,
Inflammatory marker,
Severe COVID-19,
Upper arm exercise.

Cite this as:
Tarigan AP, Listyoko AS, Pandia P, *et al.* Effects of Upper Arm and Breathing Exercise on Interleukin-6 in COVID-19 Patients. *J Respi* 2024; 10: 36-41.

ABSTRACT

Introduction: COVID-19 disease has become a comprehensive world issue and has been declared a significant threat to global health. Interleukin-6 (IL-6) is an important inflammatory marker and one of the triggers of the cytokine storm in COVID-19, where increased levels can be an independent predictor of COVID-19 mortality. This study aimed to observe the effect of upper arm and breathing exercises on IL-6 levels in severe COVID-19 patients.
Methods: The study design was quasi-experimental, with blood tests conducted before and after the examination. A total of 20 patients with confirmed COVID-19 were involved, divided into intervention and control groups.
Results: Blood tests to determine baseline IL-6 levels were performed in all patients. Patients from the intervention group were given upper arm and breathing exercises for ten days, twice a day, via video tutorials on mobile phones, while patients from the control group did not receive any exercises. Patients from the intervention group obtained mean pre- and post-exercise IL-6 levels of 42.38 ± 48.48 and 16.78 ± 18.29, respectively (p = 0.005).
Conclusion: Upper arm and breathing exercises showed significant changes in IL-6 levels in severe COVID-19 patients.

INTRODUCTION

China's Wuhan was the origin of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019. Since then, the virus has spread rapidly throughout the world and has become a global health threat. The disease that causes pneumonia infection, known as coronavirus disease 2019 (COVID-19), poses a significant danger to global health.[1] COVID-19 can trigger a cytokine storm in lung tissue through hyperactivation of the immune system and unregulated release of cytokines.[2] The term "cytokine storm" is a description of a variety of conditions that can lead to multi-organ failure and death.

The increase in pro-inflammatory cytokines in COVID-19 patients, such as interleukin-6 (IL-6), triggers inflammatory cell infiltration in lung tissues, which can damage the lung endothelium and its surroundings. IL-6 is an important inflammatory marker that can trigger a cytokine storm and is routinely checked in COVID-19 cases. Elevated IL-6 levels can be identified as an independent predictor of death from COVID-19.[3–5] A study in 2020 on the effects of upper arm and breathing exercises in chronic obstructive pulmonary disease (COPD) patients showed that a short-term combination of arms training and pursed-lip breathing had a positive impact on forced vital capacity (FVC), functional capacity, dyspnea scale, and quality

*Corresponding author: amira@usu.ac.id

Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v10-I.1.2024.36-41

of life.[6] These exercises can also be given independently to COVID-19 patients. Upper arm and breathing exercises can improve chest expansion, strengthen respiratory muscles, reduce sputum accumulation, and increase respiratory capacity. Breathing exercises also help reduce inflammation in respiratory tracts and lungs.[7,8] Several studies designing exercise strategies for SARS patients have been conducted and published. Skeletal muscle contraction stimulates the production and release of cytokines and peptides from myocytes, known as "myokines." The first myokine released into the bloodstream in response to exercise is IL-6. Contrary to popular belief, IL-6 is not a proinflammatory cytokine. Instead, it mediates anti-inflammatory responses and metabolic adaptations. By improving lipid and glucose metabolism and suppressing pro-inflammatory cytokines, IL-6 can reduce the incidence of cardiovascular disease.[9,10]

Exercise increases plasma concentrations of several cytokines, including IL-6. The first study by Steenberg, *et al.*, as cited by Lasky, *et al.* (2021), showed that skeletal muscle activity caused by exercise can increase plasmatic IL-6 levels.[11] Other studies revealed that the increase in plasma IL-6 originating from muscle fibers caused by exercise was correlated with various factors, including the duration and intensity of physical activity.[12] In addition to the direct impact of exercise on increasing plasma IL-6 levels, the study also reported that prolonged exercise followed by a protocol reduced baseline IL-6 levels over time.[13] Other factors, such as participants' physical fitness level, were also correlated with the length and intensity of physical exercise.[14] Individuals who engage in regular physical activity have lower baseline IL-6 levels than sedentary individuals.[15] Similar studies suggest that pro- and anti-inflammatory cytokines must be balanced for the immune system to modulate and consolidate neural network reorganization, as well as have positive or negative effects on brain neuroplasticity.[16] This can also be used as a reference for providing exercise for COVID-19 patients who are active or in the recovery period.[9] There is not much research on exercise in COVID-19 patients. Therefore, this study aimed to observe the effect of upper arm and breathing exercises on IL-6 levels as a marker of inflammation in severe COVID-19 patients treated in isolation rooms.

METHODS

This study was conducted at Haji Adam Malik General Hospital in Medan, Indonesia, from July to November 2021. The study design was quasi-experimental with consecutive sampling techniques. The inclusion criteria of this study were hospitalized severe COVID-19 patients aged 18-75 years old, had oxygen saturation ≤95%, survived a cytokine storm, with or without comorbidities, and the patient agreed to participate in the study by signing informed consent before taking blood samples for laboratory tests, such as baseline IL-6. COVID-19 patients with high flow nasal cannula (HFNC) who experienced side effects from antiviral drugs and loss of consciousness and patients with mental health disorders were the exclusion criteria.

The authors gave instructions to the patients before starting the exercise. The authors performed safety procedures according to the World Health Organization (WHO) regulations for handling COVID-19 patients. Patients from the intervention group were given upper arm and breathing exercises for ten days, twice a day (morning and afternoon), via cellphone video tutorials. Post-laboratory tests were performed after the intervention. The Borg scale was also assessed. This study had received approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara (No. 292/KEP/USU/2021).

Univariate analysis was performed to determine the mean value and standard deviation before and after the intervention. Bivariate analysis was used to compare data before and after intervention. The Shapiro-Wilks test was performed to test the normality of the data with a p-value (<0.05). If the data was normally distributed, the analysis used a paired t-test. If the data was not normally distributed, the Wilcoxon test was used. The collected data was processed using Statistical Package for the Social Sciences (SPSS) version 23 software.

RESULTS

Table 1 shows that the youngest patient in the intervention group was 30 years old, and the oldest was 74 years old. Furthermore, in the control group, the youngest and oldest subjects were 28 and 69 years old, respectively. The characteristics between the intervention and control groups based on age, Borg scale, saturation, and initial IL-6 levels did not show statistically significant differences.

Table 1. Respondents' characteristics distribution based on age, gender, Borg scale, saturation, and IL-6 level

	Mean ± SD		Min-Max		p*
	Intervention	Control	Intervention	Control	
Age	54.4 ± 12.94	55.7 ± 11.64	30-74	28-69	0.816
Gender: Female	0	0	0	0	
Male	10	10	10	10	
Borg scale	7.6 ± 1.2	8 ± 1.8	7-10	5-10	0.383
Saturation	86.2 ± 5.6	88.4 ± 5.3	76-92	74-92	0.576
IL-6 level	42.3 ± 48.4	90.34 ± 151.56	5.6-154.9	8.9 - 454.70	0.496

*p-value from Wilcoxon test, considered significant if $p < 0.05$

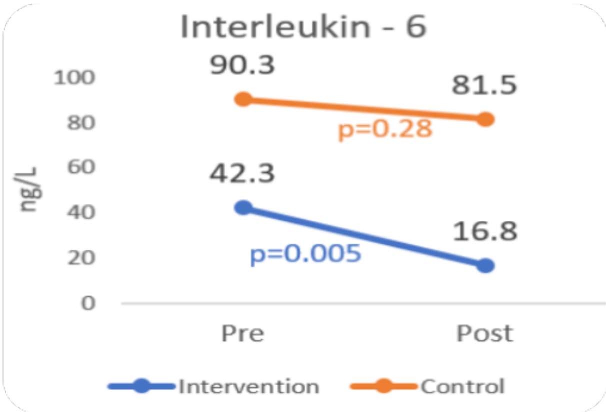

Figure 1. Pre- and post-test IL-6 level (intervention and control group)

Figure 1 shows a significant reduction in IL-6 levels in 10 COVID-19 patients in the intervention group who underwent upper arm and breathing exercises, with average IL-6 levels of 42.3 and 16.8, pre-and post-exercise, respectively ($p = 0.005$). Meanwhile, patients from the control group had lower IL-6 levels pre-and post-test, from 90.3 to 81.5. However, it was not statistically significant ($p = 0.28$).

Figure 2. (a) Upper arm exercise, (b) Breathing exercise

The picture was taken when the intervention group subjects received an explanation about the upper arm and breathing exercises in the isolation room.

Table 2. Comparison of pre-and post-test IL-6 level on intervention and control group

	Mean ± SD Intervention		Mean ± SD Control		p
	Pre Treatment	Post Treatment	Pre Treatment	Post Treatment	
IL-6	42.38 ± 48.48	16.78 ± 18.29	90.34 ± 151.56	81.55 ± 141.71	0.028

Table 2 shows a significant difference in IL-6 levels between the intervention group that was given exercise and the control group that did not receive treatment ($p = 0.028$).

DISCUSSION

In this study, an increase in the inflammatory mediator IL-6 was observed, which was associated with a decrease in the production of adaptive immunity, commonly known as the specific immune system. The specific immune system is a specific immune response to certain antigens that works more actively against infection.[10] If the virus that enters is new (no existing memory in the immune system) with high pathogenicity, then the release of cytokines will tend to leave the control body. This is known as a cytokine storm, which is a systemic inflammatory response triggered by several factors, such as a viral infection. Of all the pro-inflammatory cytokines, IL-6 is the main cause of cytokine storms. Cytokine storms can cause further complications, various abnormalities, and even malfunction of various organs, and IL-6 is one of the cytokines that provides an early indication. Examination of IL-6 levels can predict the severity of diseases caused by inflammation, autoimmune, and infections (viruses, bacteria, or other pathogens, including COVID-19).[4,5]

IL-6 is associated with severe disease and is considered a good indicator of the severity and prognosis of disease caused by SARS-CoV-2.[17,18] Elevated IL-6 levels are considered a reliable indicator of oxygen consumption, intubation, or death in individuals suffering from this disease.[19] In a retrospective analysis, Gorham, *et al*., as cited by Hirano (2021), assessed the differences in IL-6 concentrations between patients admitted to the intensive care unit (ICU) and those who did not survive. Between the two groups, the authors observed significant differences in IL-6 levels, as evidenced by significantly higher levels in the non-survivor group (720 pg/mL) compared to the survivor group (336 pg/mL). They proposed that in critically ill patients caused by SARS CoV-2, IL-6 should be re-evaluated as a sign of poor prognosis.[20]

Although IL-6 plays an important role in cerebrospinal fluid (CSF) pathophysiology during COVID-19, several related questions remain unanswered. These concerns include the appropriate use of IL-6 inhibitors in treatment, as well as assessment of disease risk, treatment options, outcomes, and adverse drug reactions. Studies on the identification of additional therapeutic targets relevant to the treatment of cytokine storm syndrome (CSS) in COVID-19 patients are necessary for the development of personalized immunomodulatory therapies, considering the role of cytokines in pathogenesis. The targets of this treatment include activation of the complement system and inhibition of IL-1, IL-6, TNFα, GM-CSF, IFNγ, IL-17, and IL-18.[21]

The release of IL-6 from respiratory epithelial cells, $CD14^{+}CD16^{+}$ monocyte macrophages, and lymphocytes after infection may be the mechanism underlying the increase in IL-6 in COVID-19 patients.[22,23] SARS-CoV-2 enters the body during COVID-19 and causes excessive activation of immune cells, leading to the production of various inflammatory factors and inflammatory cytokine storms. Ultimately, these events lead to multiple organ failure, acute respiratory distress syndrome (ARDS), and systemic inflammatory response syndrome (SIRS), which is characterized by high fever, dyspnea, lymphopenia, and increased cytokines.[24]

The data obtained in this study showed the presence of infection and cytokine storm in COVID-19 patients. It appeared due to hyper-inflammatory responses, indicated by the excessive release of IL-6 proinflammatory cytokines and coagulopathy characterized by an increase in D-dimmer. IL-6 is an inflammatory cytokine found to increase during COVID-19 infection. Furthermore, pro-inflammatory cytokine is synthesized by lung parenchyma cells, and an increase in level indicates severe inflammation condition in the lungs.[12]

IL-6 is a pleiotropic cytokine that regulates immune and inflammatory responses.[11] IL-6 levels in the acute phase reflect inflammatory conditions in the lungs. Several studies have been conducted regarding the role of IL-6 as a predictor of COVID-19, as well as a predictor of prognosis in severe cases.[13]

In this study, the IL-6 level in severe COVID-19 patients was 42.38 ng/L. Increased IL-6 levels were associated with more severe and worse conditions in acute COVID-19 patients. In addition, higher baseline IL-6 values were associated with worse chest CT imaging, and patients with severe infections required more intensive treatment.[13]

This study is similar to the study of Liu, *et al*. (2020), which showed that the increase in IL-6 levels was significantly higher in severe COVID-19 patients.[17] IL-6 is synthesized by various lung cells, such as alveolar macrophages, pneumocytes, and fibroblasts. IL-6 levels reflect inflammatory conditions in the lungs. Increasing IL-6 is associated with disease severity, as levels decrease when remission occurs and increase when the infection worsens. Hyperactivity of IL-6 in COVID-19 patients can cause complications, such as respiratory failure, shock, and multi-organ perfusion. Managing control of inflammation, including IL-6, has become part of treating COVID-19. Therefore, IL-6-targeted treatment is effective in resolving the cytokine storm during the progression of COVID-19 infection.[14,15]

The clinical manifestations of COVID-19 infection vary greatly, ranging from asymptomatic to severe or critical. Shortness of breath is one of the typical symptoms of COVID-19, which can quickly turn into a critical condition, such as acute respiratory distress. Shortness of breath in COVID-19 infection occurs due to difficulty perfusion and oxygen diffusion in the lungs due to inflammation caused by the virus.[12]

The goal of upper arm and breathing exercises is to increase chest expansion and respiratory muscle performance. Moreover, this exercise is also performed to strengthen the respiratory muscles of COVID-19 patients. Therefore, they can reduce the buildup of phlegm, which will bring their respiratory capacity up to standard. Upper arm and breathing exercises can be performed independently by COVID-19 patients and help maintain lung function. Hence, the hardening of lung tissue can be reduced.[6]

Upper arm and breathing exercises consist of a series of exercises to regulate rhythm, allow better chest expansion, activate the supporting muscles of the chest cavity or chest wall, and train the main muscles of breathing. In addition, this exercise can help reduce inflammation in the airways and lungs. Regular physical activity for COVID-19 patients can improve the immune system and increase the production of antibodies and T cells, thus improving blood circulation. This routine will also reduce stress hormones, adrenaline, and cortisol, which gives extra strength to the immune system. Furthermore, it can also reduce the risk of respiratory tract infections.[16]

In this study, initial examination showed an increase in IL-6 levels in the blood of COVID-19 patients. Upper arm and breathing exercises in the intervention group showed a significant difference in IL-6 levels compared to the control group, $p = 0.028$. Additionally, a significant reduction in IL-6 levels was observed in the intervention group from 42.3 to 16.8.

Regular, scheduled, and correct exercise in COVID-19 patients can increase body endurance. Many studies have proven that exercise can improve immune function. This will increase immune surveillance against pathogens and reduce systemic inflammation, such as IL-6, complement, and immunoglobulin.[17]

The immune response to physical exercise depends on the intensity and duration of the exercise. At moderate-intensity exercise of less than 60 minutes, there is increased immune surveillance of immune cell subtypes, which provides therapeutic and preventive effects. This acute response to moderate exercise includes increased antipathogenic activity of macrophages concomitant with increases in circulating immunoglobulins and anti-inflammatory cytokines. If the exercise is performed regularly, an initial, temporary increase in lymphocytes will improve immune surveillance and reduce systemic inflammation.[16]

CONCLUSION

Significant improvement in IL-6 levels occurred in severe COVID-19 patients treated with upper arm and breathing exercises. This study can be a reference for other researchers to conduct further research on post-COVID-19 patients and other respiratory patients who exercise.

Acknowledgments
The author would like to thank all staff at the Laboratory and Department of Pulmonology and Respiratory Medicine at Haji Adam Malik General Hospital, Medan, Indonesia, for their assistance during the study.

Conflict of Interest
The authors declared there is no conflict of interest.

Funding
This study was funded by Research TALENTA Universitas Sumatera Utara budget year 2021 Fiscal Year in accordance with the Research Contract Amendment Number: 323/ UN5.2.3.1/ PPM/ SPP USU TALENTA / 2021.

Authors' Contributions
Designed the study and methodology: NCBP. Literature reading: APT, PCE. Review of the datasets: APT. Manuscript writing: PP, SPS, EE. Presentation of the article: PP, SPS, EE. Data collection and analysis: AP. All authors contributed and approved the final version of the manuscript.

REFERENCES

1. Wang D, Hu B, Hu C, *et al*. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061–1069. [PubMed]
2. Zhou F, Yu T, Du R, *et al*. Clinical Course and Risk Factors for Mortality of Adult Inpatients with COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet* 2020; 395: 1054–1062. [PubMed]
3. World Health Organization (WHO). *Clinical Management of Severe Acute Respiratory Infection when Novel Coronavirus (nCoV) Infection is Suspected*. Geneva, https://www.who.int/publications/i/item/10665-332299 (2020).
4. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A Systematic Review and Meta-Analysis. *Rev Med Virol* 2020; 30: 1–9. [PubMed]

5. Danwang C, Endomba FT, Nkeck JR, *et al*. A Meta-Analysis of Potential Biomarkers associated with Severity of Coronavirus Disease 2019 (COVID-19). *Biomark Res* 2020; 8: 37. [PubMed]
6. Tarigan AP, Ananda FR, Pandia P, *et al*. The Impact of Short-term Combination of Limb Training and Pursed-lip Breathing in Chronic Obstructive Pulmonary Disease. *Open Access Maced J Med Sci* 2020; 8: 479–483. [Journal]
7. Zhao H-M, Xie Y-X, Wang C. Recommendations for Respiratory Rehabilitation in Adults with Coronavirus Disease 2019. *Chin Med J (Engl)* 2020; 133: 1595–1602. [PubMed]
8. Yang L-L, Yang T. Pulmonary Rehabilitation for Patients with Coronavirus Disease 2019 (COVID-19). *Chronic Dis Transl Med* 2020; 6: 79–86. [PubMed]
9. Cui W, Ouyang T, Qiu Y, *et al*. Literature Review of the Implications of Exercise Rehabilitation Strategies for SARS Patients on the Recovery of COVID-19 Patients. *Healthcare*; 9. Epub ahead of print 2021. [PubMed]
10. Rosyanti L, Hadi I. Respon Imunitas dan Badai Sitokin Severe Acute Respiratory Syndrome Corona Virus 2 : Literatur Review. *J Kesehat Madani Med* 2020; 11: 176–201. [Journal]
11. Lasky JA, Fuloria J, Morrison ME, *et al*. Design and Rationale of a Randomized, Double-Blind, Placebo-Controlled, Phase 2/3 Study Evaluating Dociparstat in Acute Lung Injury Associated with Severe COVID-19. *Adv Ther* 2021; 38: 782–791. [PubMed]
12. Perrone F, Piccirillo MC, Ascierto PA, *et al*. Tocilizumab for Patients with COVID-19 Pneumonia. The Single-Arm TOCIVID-19 Prospective Trial. *J Transl Med* 2020; 18: 405. [PubMed]
13. Lescure F-X, Honda H, Fowler RA, *et al*. Sarilumab in Patients Admitted to Hospital with Severe or Critical COVID-19: A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Respir Med* 2021; 9: 522–532. [PubMed]
14. Guaraldi G, Meschiari M, Cozzi-Lepri A, *et al*. Tocilizumab in Patients with Severe COVID-19: A Retrospective Cohort Study. *Lancet Rheumatol* 2020; 2: e474–e484. [PubMed]
15. Tania POA, Simamora D, Parmasari W, *et al*. Kadar Interleukin 6 (IL-6) sebagai Indikator Progresivitas Penyakit Reumatoid Arthritis (RA). *J Ilm Kedokt Wijaya Kusuma* 2014; 3: 40. [Journal]
16. Wardika IK, Sikesa IGPH. Pengukuran Interleukin-6 (IL-6), C-Reactive Protein (CRP) dan D-Dimer sebagai Prediktor Prognosis pada Pasien COVID-19 Gejala Berat: Sebuah Tinjauan Pustaka. *Intisari Sains Medis* 2021; 12: 901–907. [Journal]
17. Liu T, Zhang J, Yang Y, *et al*. The Role of Interleukin-6 in Monitoring Severe Case of Coronavirus Disease 2019. *EMBO Mol Med* 2020; 12: e12421. [PubMed]
18. Vepa A, Bae JP, Ahmed F, *et al*. COVID-19 and Ethnicity: A Novel Pathophysiological Role for Inflammation. *Diabetes Metab Syndr* 2020; 14: 1043–1051. [PubMed]
19. Bohn MK, Hall A, Sepiashvili L, *et al*. Pathophysiology of COVID-19: Mechanisms Underlying Disease Severity and Progression. *Physiology (Bethesda)* 2020; 35: 288–301. [PubMed]
20. Hirano T. IL-6 in Inflammation, Autoimmunity and Cancer. *Int Immunol* 2021; 33: 127–148. [PubMed]
21. Apituley TLD, Pangemanan DHC, Sapulete IM. Pengaruh Olahraga terhadap Coronavirus Disease 2019. *J Biomedik JBM* 2021; 13: 111–117. [Journal]
22. Hammami A, Harrabi B, Mohr M, *et al*. Physical Activity and Coronavirus Disease 2019 (COVID-19): Specific Recommendations for Home-Based Physical Training. *Manag Sport Leis* 2022; 27: 26–31. [Journal]
23. Mohamed AA, Alawna M. Role of Increasing the Aerobic Capacity on Improving the Function of Immune and Respiratory Systems in Patients with Coronavirus (COVID-19): A Review. *Diabetes Metab Syndr* 2020; 14: 489–496. [PubMed]
24. Prabawa IMY, Silakarma D, Manuaba IBAP, *et al*. Chest Therapy and Breathing Exercise in COVID-19 Patient: A Case Report. *Bali Med J* 2021; 10: 495–498. [Journal]