Prevention and Rehabilitation

The effect of aerobic exercise on immune biomarkers and symptoms severity and progression in patients with COVID-19: A randomized control trial

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ABSTRACT

Background: The World Health Organization in March 2020 has announced that COVID-19 is a world pandemic because the number of infected cases increases rapidly. however, there are several available vaccines, their protection is limited to a certain period. Thus, the role of modalities that improve immune functions should be performed to counter COVID-19 viral load and decrease mortality rates.
Objective: To investigate the effect of aerobic exercise on immune biomarkers, disease severity, and progression in patients with COVID-19.
Design: A randomized controlled study.
Participants: Thirty patients with COVID-19 participated in this study. Participants' age ranged from 24 to 45 years old. Participants had a mild or moderate COVID-19. Participants were assigned randomly into two groups, exercise and control groups. There were two main dependent variables including blood immune markers and severity of respiratory symptoms.
Interventions: All participants performed 2 weeks of moderate-intensity aerobic exercise for 40 min/session, 3 sessions/week. The measurements were performed at baseline, and after 2-weeks.
Results: At baseline measurements, there were non-significant differences between both groups in the Wisconsin scale total score, Leucocytes, Lymphocytes, Interleukin-6, Interleukin-10, Immunoglobulin-A, and TNF-α (P > .05). After the intervention, the Wisconsin scale (patient-oriented illness-specific quality-of-life) total score significantly decreased in the intervention group (P < .05); while, Leucocytes, Lymphocytes, and Immunoglobulin-A significantly increased in the intervention group (P < .05).
Conclusion: The current study indicated that 2 weeks of moderate-intensity aerobic exercise decreased the severity and progression of COVID-19 associated disorders and quality of life. Also, a 2-weeks of aerobic exercise positively affected immune function by increasing the amounts of Leucocytes, Lymphocytes, Immunoglobulin A.

1. Introduction

At the end of 2019, a series of unknown-cause pneumonia cases have appeared in Wuhan (Hubei, China) (Lu et al., 2020). A lower respiratory tract deep analysis revealed that the cause of this pneumonia was due to a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Huang et al., 2020) or

(COVID-19). The World Health Organization in March 2020 has announced that COVID-19 is a world pandemic because the number of infected cases increased rapidly (WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 11 March 2020, n.d.). Until the 27th of October 2020, according to WHO, there were approximately 42, 966, 344 confirmed cases of COVID-19, with 1,152,604 deaths (WHO Coronavirus Disease (COVID-19) Dashboard, n.d.; World Health Organization (WHO), 2020).

COVID-19 is a type of coronaviruses with an enveloped RNA. Its RNA is considered the largest known RNA genomes-30-32 kb-with a 50-cap structure and 30-poly-A tail (Di Gennaro et al., 2020; Guan et al., 2020). The median age of COVID-19 infected individuals is 47

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years (Guan et al., 2020). Fever and cough are common symptoms in COVID-19 with existing rates of 43.8% and 67.8% respectively (Guan et al., 2020). Other symptoms seen in patients with COVID-19 are loss of taste, myalgia, fatigue, and dyspnea (Cascella et al., 2020). However, SARS-CoV and MERS-CoV, and SARS-CoV-2 rise from the same natural origin which is bats (Fani et al., 2020), COVID-19 is more dangerous because it has a rapid spread rate (Fani et al., 2020). The adaptation of the S-glycoprotein and its affinity for ACE2 can determine the severity of SARS-CoV-2 infection (Fani et al., 2020). SARS-CoV-2 S protein to ACE2 is 10–20 more than the SARS-CoV-1. Also in COVID-19, the viral load early peaks in the nose and throat after the development of symptoms; while in SARS-Co-1, the viral load peaks much later in the illness (Al-Tawfiq, 2020). These findings document the theory of the higher contamination of SARS-CoV-2 in comparison with SARS-CoV(Fani et al., 2020). This might indicate the more important role of the immune system as an early defense to prevent its high contamination.

Patients with COVID-19 present with a severe reduction in serum T cells, CD4$^+$, CD8$^+$ T cells, and B-cells, particularly those who need an intensive care unit. previous studies found that the total T cells, CD4$^+$ T cells, or CD8$^+$ T cells are less than 800, 400, or 300/μL, respectively, and these are inversely correlated with the patient's survival rate (Diao et al., 2020; Xu et al., 2020). As a compensatory mechanism, the body increases serum CRP, IL-6, IL-10, TNF-α, and immunoglobins (IgA, IgM, and IgG) to counteract COVID-19 (Chao et al., 2020; Xu et al., 2020). IgA plays a critical role in humoral immunity and it is the most critical immunoglobulin to fight viruses in the respiratory and digestive systems at the point of virus entrance. IgA can neutralize the COVID-19 virus earlier to its reaching and binding to epithelial cells (Chao et al., 2020). Thus, recent immunotherapy strategies try to obtain high serum virus-specific immunoglobulins to neutralize the virus through an active increase of host immune reaction (active immunization) or passive increase of these levels by plasma from recovered patients (Chao et al., 2020).

Aerobic exercise produces an immediate enhancement in immune functions (ALAWNA et al., 2021; Amro et al., 2021; Mahmoud Mohamed and Alawna, 2020; Mohamed et al., 2020; Mohamed and Alawna, 2020, 2021), and this might play a major role in the treatment and prevention of COVID-19 (Dixit, 2020). This can be produced through four main mechanisms: 1) It increases the number of immune markers including, neutrophils, monocytes, T-lymphocytes, and macrophages which are crucial elements that play a major role in human defense against infections (Gonçalves et al., 2020; Li and Cheng, 2007; G. Lippi et al., 2010; Giuseppe Lippi et al., 2014; Lira et al., 2017; Reis Gonçalves et al., 2012). 2) It helps to increase the number of serum immunoglobulins (IgA, IgM, IgG), which plays a major role against lung infections, especially IgA(Cunningham-Rundles, 2009; Hines et al., 1996; G. Mohamed and Taha, 2016; Rodríguez et al., 2005). 3) It helps to regulate the level of C-reactive proteins by producing a short-term minor elevation to help in fighting lung infections (De Gonzalo-Calvo et al., 2015; Marklund et al., 2013; B. K. Pedersen and Hoffman-Goetz, 2000), and a long-term reduction to help in inhibiting any reduction in lung functions (Okita et al., 2004; Zheng et al., 2019). 4) It reduces anxiety and depression which can improve immune functions through an autonomic modulation (Broman-Fulks and Storey, 2008; Chan et al., 2019; Crabbe et al., 2007; Hogan et al., 2013; Marshall, 2011; Nabkasorn et al., 2006; Reed and Buck, 2009).

Several studies have shown the protective and curative roles of aerobic exercise in lung infections. Barrett et al. (2018) investigated the effect of aerobic exercise on the prevention of acute respiratory infection in patients with an acute respiratory infection (MEPARI-2). They found that aerobic exercise significantly decreased the episodes, duration, and severity of infections. They also observed

that aerobic exercise significantly increased serum interleukin-8 and neutrophils. Toledo et al. (2012) studied the effects of 24-weeks mild aerobic exercise on the incidence of pulmonary diseases in rodents. They used the reactive oxygen species as an indicator of the initiation of lung infections. They found that mild aerobic exercise decreased reactive oxygen species concentration in the bronchoalveolar lavage fluid in rodents; which is very important to inhibit or reduce the progression of pneumonia and acute respiratory distress syndromes commonly develop with lung infections (Toledo et al., 2012).

COVID-19 highly spreads across the world and the development of an effective treatment against its COVID- 19 derivatives might take a long period, thus the role of the modalities that improve immune functions should be performed to counter COVID-19 viral load and decrease its mortality rates. To the best of our knowledge, no study investigated the effect of aerobic exercise on patients with COVID-19. Thus, this study aimed to investigate the effect of aerobic exercise on immune biomarkers and disease severity and progression in patients with COVID-19.

2. Method

2.1. Study design

A pilot randomized controlled design was used. Each participant was asked to sign an informed consent earlier to participating in this study. This study was approved by the ethics committee of the School of Health Sciences, Istanbul Gelisim University, Turkey. Patients were recruited from April 2020 to June 2020. The participants were collected through reviewing the Turkish hospital's data in Istanbul and persons who were diagnosed with COVID-19 have been contacted with a phone call to ask them for their welling to participate in this study. The participants, who accepted the participation, were interviewed through video calls using Zoom App to discuss study procedures with them. The participant who accepted to engage in this study was visited by a researcher at home while they are in the quarantine, at this visit the patients signed the consent form, and blood samples were taken. All participants had a medical clearance and permission to perform the aerobic exercise from their physicians (the physician who supervised and diagnosed the patient with COVID-19). The clinical protocol of this study was registered at https://www.clinicaltrials.gov/ platform und this registration number NCT04581291.

2.2. Participants' recruitments

We conducted a priori power test to determine the suitable sample size for our study. The G*POWER program (ver. 3.1.9.2, Heinrich-Heine-University, Düsseldorf, Germany) was used. The criteria introduced to the program included a MANOVA test using 2 groups, 2 measurements, a power level of 80%, a significance level of 0.05, and medium effect size (dz = 0.25) (Faul et al., 2007). Based on the aforementioned assumptions, the total sample size needed for this study was 30 patients. A minimum power of 80% or more should be used because it is acceptable in most studies (Kadam and Bhalerao, 2010). The flow of participants throughout the study is shown in Fig. 1.

Thirty patients with COVID-19 participated in this stud. Participants' age ranged from 24 to 45 years old. The inclusion criteria included that the patient had a recent mild or moderate COVID-19 with no or low-grade fever 99.5–100.94 °F (37.5–38.3 °C) (Affronti et al., 2010; Zhuang et al., 2020). Mild COVID-19 included that the patient had symptoms of acute upper respiratory tract infection (fever, cough, myalgia, runny nose, fatigue, sore throat, sneezing) or gastrointestinal symptoms (nausea, vomiting, abdominal pain,
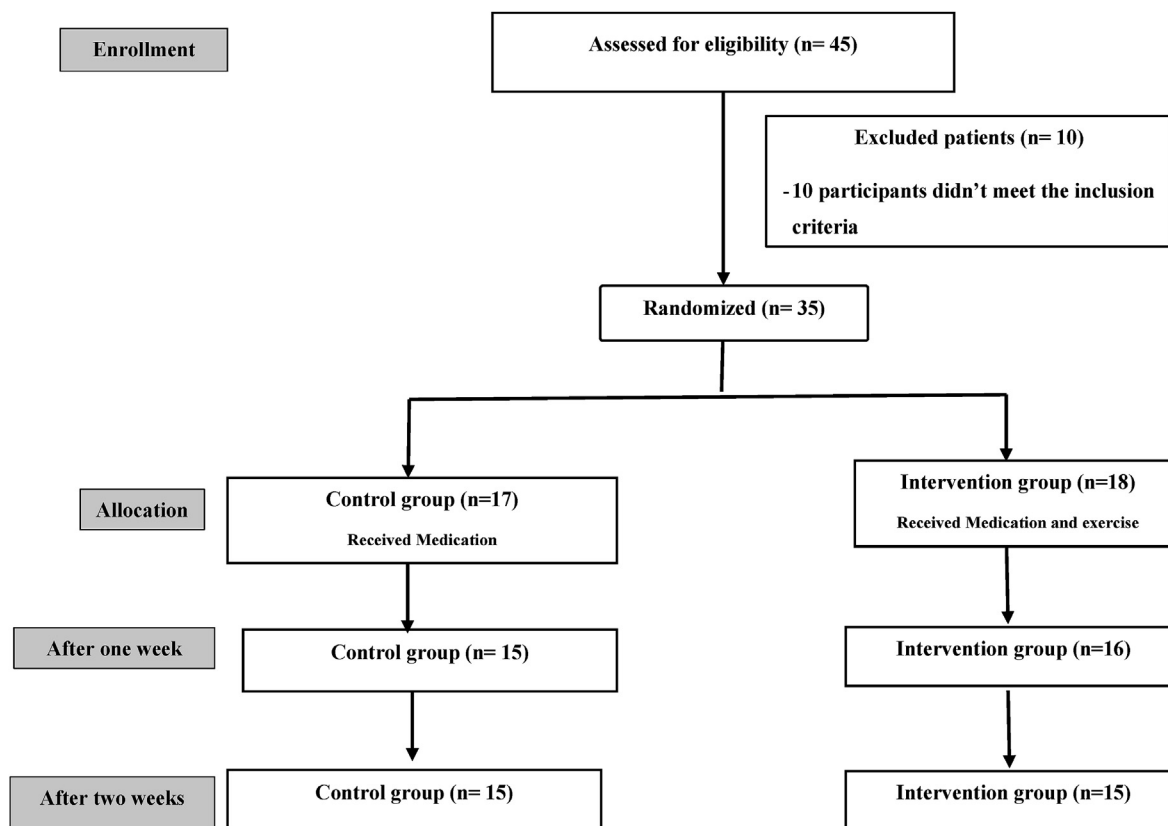
Fig. 1. Patients flow chart.

diarrhea). Moderate grade of COVID 19 included that the participant had pneumonia (cough, frequent fever) with no obvious hypoxemia, the presence of lesions on chest CT (Yuki et al., 2020). The exclusion criteria included that patient was not hospitalized and had high-grade fever <100.94 °F (<38.3 °C) or other chronic diseases such as heart problems, hypertension, or diabetes. Women how were using contraceptives were excluded because contraceptives decrease immune functions and might affect the subjectivity to autoimmune disorders with marked increases in risk for various autoimmune disorders (Williams, 2017).

2.3. Evaluative procedures

There were two main dependent variables including blood immune markers and severity of respiratory symptoms. These measurements were collected at the baseline and 24 h after the end of the exercise program (two weeks).

A lab technician was asked to visit the patient at home (quarantine). The lab technician wore special protective equipment recommended by WHO(WHO, 2020b; World Health Organization (WHO), 2020). Two visits were performed, one at the beginning of the research procedures, and the last visit at the 24 h after the end of the exercise program (two weeks). The technician collected blood and saliva samples to be analyzed.

3. Blood sample collection

Blood samples were taken in the morning (8:30–9:30) by collecting 10 mL of venous blood. Participants were asked to stop any exercise for at least 24 h before blood sampling. Also, participants were asked to stop eating any food or liquid from 10:00 p.m. the prior day of measurement. Samples were collected in vacutainer tubes with sodium ethylenediami-netetraacetic acid (EDTA) for plasma separation. The blood was centrifuged at 3000 rpm for 15 min at 4 °C. We measured total lymphocytes, leukocytes, and monocytes from total-blood samples utilizing a multichannel hemocyte analysis system (SE-9000; Sysmex Corp, Hyogo, Japan) (Lira et al., 2017; Shimizu et al., 2011). The concentrations of IL-6, IL-10, and TNF-α were analyzed by using ELISA commercial kits assay (R&D Systems, Minneapolis, USA) following the manufacturer's instructions for analysis on an EZ-Reader microplate reader at 450 nm (de Souza et al., 2018; Lira et al., 2017). The samples were stored at −20 °C for further analysis.

4. Saliva sample collection

A saliva sample was collected to measure the salivary IgA-S concentration. The saliva sample was taken without any saliva stimulation methods. The participant was asked to rinse their mouths with distilled water and to evacuate their mouth just before the collection. We used the passive drainage method for the collection, in which the participant slightly flexed their head forward to allow the saliva to move into a sterilized and pre-weighed Falcon tube for 5 min. The weight of tubes was measured again following the collection to estimate the volume and the saliva flow rate. The tubes were weighed with 0.1 mg accuracy with proposed saliva density as 1.0 g mL^{-1}. The samples were stored at −80 °C for further analysis. The S-IgA concentration was analyzed utilizing commercial ELISA kits (IgA Salivary, DRG, Minneapolis, USA). The IgA-S secretion rate (ng/min) was measured by multiplying the whole concentration of IgA-S present in the mucosal surface per unit of time by the saliva flow rate (mL/min) (de Souza et al., 2018).

5. Wisconsin upper respiratory symptom survey

The Wisconsin Upper Respiratory Symptom Survey (WURSS) is an empirically derived patient-oriented illness-specific quality-of-life evaluative outcomes instrument (*The Wisconsin Upper Respiratory Symptom Survey Is Responsive, Reliable, and Valid*) (Barrett et al., 2018). The development process of this survey was described in details by Barrett et al.(*The Wisconsin Upper Respiratory Symptom Survey (WURSS): A New Research Instrument for Assessing the Common Cold - PubMed*) (Barrett et al., 2018). WURSS-24 is designed to evaluate the negative effect of acute upper respiratory infection, presumed viral (the common cold). It is a validated and reliable measurement method for evaluating the change in the quality of life over time including influenza-like illness symptoms of headache, body aches, and fever (The Wisconsin Upper Respiratory Symptom Survey Is Responsive, Reliable, and Valid; Barrett et al., 2018). The participants were asked to fill the survey before starting the study and after 2 weeks.

5.1. Treatment procedures

Participants were assigned randomly into two groups, exercise and control groups. All participants in both groups followed the WHO guidelines of quarantine (WHO, 2020a) and used standardized medications given by the physician according to the Turkish Ministry of Health, including the Hydroxyclorocin Sulphate 200 Mg Film Tablet (Plaquenil 200 Mg Film Tablet). The dose was 2 times/day, 200Mg/time, for 5 days (COVID-19 Tedavi, n.d.). Besides, the exercise group performed moderate-intensity aerobic exercise for 40 min/session, 3 sessions/week, for 2 weeks.

Participants in the exercise group performed a two weeks aerobic exercise program. The exercise program consisted of walking/running on a treadmill or bicycling on a stationary bicycle. Each session is composed of a 5-min warm-up slow walking or bicycling. Then the main intervention consisted of 30 min of moderate-intensity aerobic exercise (walking/running or bicycling). Lastly, a 5-min cool-down exercise (walking/running or bicycling). The exercise intensity was 60—75% of the predicted MHR (calculated as MHR = 210—age).

The Borg Rating of Perceived Exertion (RPE) scale was used to control the exercise intensity (The Borg Rating of Perceived Exertion (RPE) Scale, 2017). RPE is a reliable and validated scale to allow individuals to monitor and guide the exercise intensity by rating their level of exertion during exercise (Crawford et al., 2018). After explaining the scale in detail for patients, we asked them to keep the exertion rating level between 12 and 14 (light — somewhat hard) on the Borg Scale, which suggests that the patient is exercising on a moderate exercise level (The Borg Rating of Perceived Exertion (RPE) Scale, 2017). The exercise was stopped if the patient experienced any of the following signs and symptoms: chest pain, shortness of breath, fainting, claudication, fatigue, ataxia, dizziness, cyanosis, or pallor (Albouaini et al., 2007).

5.2. Data analysis

Participants' files were encoded by a college administrator who did not participate in this study (Taylor and Murphy, 2010). The intention-to-treat and general linear models of analysis were followed. A multivariate of analysis for repeated measurements (MANOVA) test was followed to measure within each group interactions, while an independent MANOVA test was followed to measure between-group comparisons. The outcome measures were measured at the baseline, and 24 h after two weeks of the exercise program. All results were compared to the baseline results. In this study, the baseline characteristics of patients in the intervention and control groups were compared using Pearson chi-squared tests for categorical variables, involving gender, previous lung infection history. A *t*-test was followed for continuous variables of age and body mass index (BMI). The significance level was set at P < .05. The SPSS (ver. 25, IBM Inc., Armonk, NY, USA) was used for statistical analysis.

5.3. Results

At the baseline, there were non-significant differences between the groups in age, height, and BMI, as (P > .05). The measurement values were normally distributed in both groups (Shapiro-Wilk test, P > .05) (Rochon et al., 2012). The demographic and physical characteristics of participants at the baseline are shown in Table 1.

Between-group comparisons showed that at baseline measurements, there were non-significant differences between groups in Wisconsin scale total score, Leucocytes, Lymphocytes, Interleukin-6, Interleukin-10, Immunoglobulin-A, and TNF-α (P > .05). Wisconsin scale total score significantly decreased in the intervention group when compared to the control group after two weeks of intervention (P < .05). Leucocytes, Lymphocytes, and Immunoglobulin-A significantly increased in the intervention group in comparison to the control group after two weeks of intervention (P < .05). Interleukin-6, Interleukin-10, and TNF-α showed non-significant differences between both groups after two weeks of intervention (P > .05). The between-group comparisons are shown in Table 2 and Fig. 2.

Within-group comparisons showed that the Wisconsin scale total score significantly decreased in both groups (control and intervention) after two weeks of treatment (P < .05). Leucocytes, Lymphocytes, and Interleukin-10 significantly increased in both groups after two weeks of treatment (P < .05). After two weeks of treatment, Interleukin-6, and Immunoglobulin-A significantly increased in the intervention group (P < .05), while it showed non-significant differences in the control group (P > .05). On the other hand, TNF-α showed non-significant differences in the intervention group (P > .05), while it increased significantly in the control group (P < .05). Within-group comparison results are shown in Table 3.

6. Discussion

This study investigated the effect of performing a moderate-intensity aerobic exercise on immune biomarkers, the severity of symptoms, and disease progression in patients with COVID-19. This study is unique as it is the first clinical trial that demonstrates that aerobic exercise could be an adjunct intervention for patients with COVID-19 to enhance our immunity to counter COVID-19 infection.

Regarding the severity and progression of upper respiratory tract infection symptoms, the Wisconsin scale total score has been shown to be significantly lower in the intervention group in comparison with the control group. This difference occurred due to

Table 1
Physical characteristics of patients in all groups.

Items	Control group	Intervention group	P
	Mean ± SD	Mean ± SD	
Age (yrs.)	35.25 ± 3.96	44.56 ± 4.25	>.05
Height (Cm)	173.4 ± 5.96	176.1 ± 6.01	>.05
BMI	23.95 ± 1.21	24.65 ± 1.31	>.05
Male	7	8	>.05
Female	8	7	>.05
Smoking	3	4	>.05
Non-smoking	12	11	>.05

SD: standard deviation, P: probability, cm: centimeter, yrs: years, and *: significant.

Table 2
Independent measure MANOVA between groups of immune markers and Wisconsin scale between the baseline, and 2 weeks after intervention.

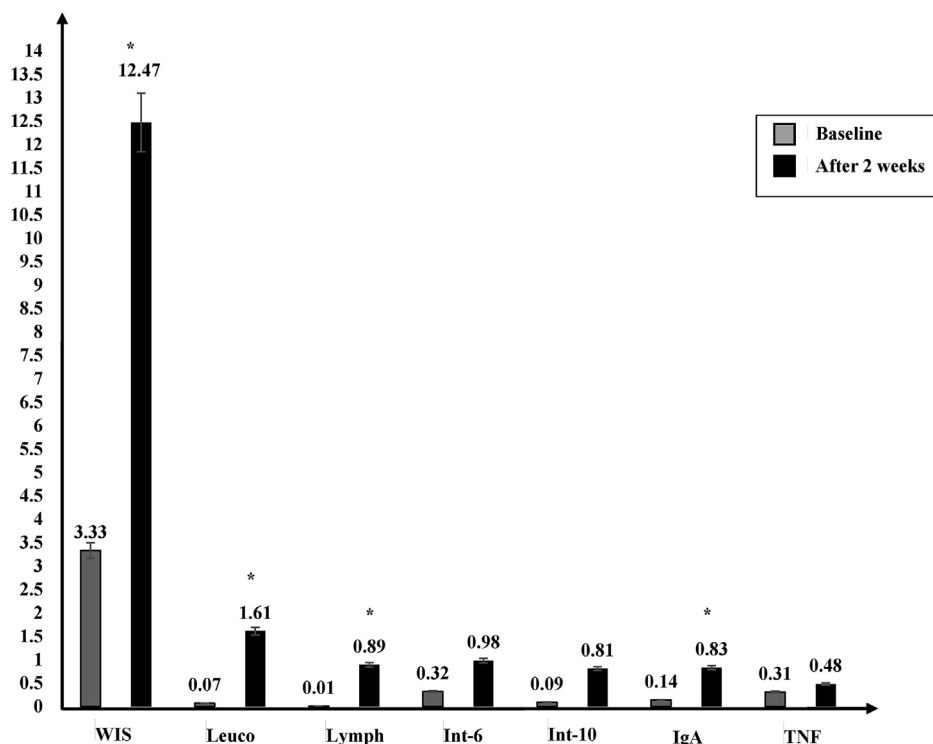|	Baseline					After 2 Weeks				
	MD±SE	95%CI	P	F	Power	MD±SE	95%CI	P	F	Power
Wisconsin scale	3.33 ± 1.96	0.68–7.35	>0.05	2.90	0.38	12.47 ± 1.99	8.39–16.55	<.01*	39.18	1.00
Leucocytes, × 109/L	0.07 ± 0.49	0.94–1.08	>0.05	0.02	0.05	1.61 ± 0.51	0.57–2.64	<.01*	10.12	0.87
Lymphocytes, × 109/L	0.01 ± 0.07	0.14–0.15	>0.05	0.01	0.05	0.89 ± 0.07	0.75–1.04	<.01*	15.25	1.00
Interleukin-6, pg/mL	0.32 ± 4.22	8.33–8.97	>0.05	0.01	0.05	0.98 ± 4.26	4.73–12.70	>0.05	0.88	0.15
Interleukin-10, pg/mL	0.09 ± 0.44	0.82–0.99	>0.05	0.04	0.05	0.81 ± 0.43	0.08–1.70	>0.05	3.51	0.44
Immunoglobulin A, g/L	0.14 ± 0.15	0.17–0.44	>0.05	0.85	0.14	0.83 ± 0.17	0.48–1.18	<.01*	23.13	0.99
TNF-α	0.31 ± 0.29	0.29–0.90	>0.05	1.10	0.17	0.48 ± 0.31	0.15–1.11	>0.05	2.45	0.33

Fig. 2. Independent measure MANOVA between groups between the baseline and 2 weeks after intervention. WIS: Wisconsin scale, Leuco: Leucocytes, Lymph: Lymphocytes, Int-6: Interleukin-6, Int-10: Interleukin-10, IgA: Immunoglobulin A, TNF: TNF-α., and *: significance. there were significance difference between the intervention groip and control group for Wisconsin scale, Leucocytes, Lymphocytes, and Immunoglobulin A.

Table 3
Repeated measure MANOVA of immune markers and Wisconsin scale between the baseline, and 2 weeks after intervention.

	Group	Baseline	After 2 Weeks		
		M±SD	M±SD	95%CI	P
Wisconsin scale	Control group	110.33 ± 5.41	104.13 ± 5.82	4.91–7.50	<.01*
	Intervention group	107.00 ± 5.32	91.67 ± 5.07	13.60–17.07	<.01*
Leucocytes, × 109/L	Control group	5.37 ± 1.37	5.74 ± 1.37	0.26–0.47	<.01*
	Intervention group	5.44 ± 1.32	7.34 ± 1.40	1.66–2.14	<.01*
Lymphocytes, × 109/L	Control group	0.97 ± 0.20	1.20 ± 0.22	0.16–0.29	<.01*
	Intervention group	0.98 ± 0.19	2.09 ± 0.18	0.98–1.25	<.01*
Interleukin-6, pg/mL	Control group	22.73 ± 11.53	23.01 ± 11.45	0.07–0.61	>0.05
	Intervention group	23.05 ± 11.60	26.99 ± 11.86	3.25–4.63	<.01*
Interleukin-10, pg/mL	Control group	6.09 ± 1.19	6.23 ± 1.19	0.02–0.27	<.03*
	Intervention group	6.18 ± 1.23	7.04 ± 1.17	0.70–1.03	<.01*
Immunoglobulin A, g/L	Control group	2.25 ± 0.39	2.35 ± 0.51	0.01–0.27	>0.05
	Intervention group	2.38 ± 0.42	3.18 ± 0.43	0.65–0.94	<.01*
TNF-α	Control group	10.21 ± 0.82	10.78 ± 0.82	0.44–0.68	<.01*
	Intervention group	10.52 ± 0.78	11.25 ± 0.86	0.27–1.20	>0.05

M: Mean, SD: Standard deviation, CI: Confidence interval, P: Probability, and *: Significant.

several mechanisms. First, moderate aerobic exercise significantly increases the activity of neutral killer cells (NK), especially during exercise. NK plays a major role against upper respiratory tract infection which leads to a decrease in the severity and progression of symptoms (De la Fuente et al., 1993; Murphy et al., 2004; Sugiura et al., 2001). Second, aerobic exercise increases the amount and activity of macrophages (De la Fuente et al., 1993; Murphy et al., 2004; Sugiura et al., 2001). The increase in macrophages increases respiratory immunity to virus growth, inactivates the extracellular virus, and suppresses virus replication in the respiratory tract, lungs, or adjacent cells (De la Fuente et al., 1993; Murphy et al., 2004; Sugiura et al., 2001; Wu and Morahan, 1992). Also, the increase in macrophages increases the production of chemokines and antiviral factors such as TNF-α and IFN-α/β that help to recruit and activate other cell types to combat viral infections (Murphy et al., 2004; Wu and Morahan, 1992). Third, moderate-intensity aerobic exercise increases the concentration of salivary immunoglobulin (Ig) A, which have a converse relationship with the risk and severity of the upper respiratory tract infection symptoms (De la Fuente et al., 1993; Murphy et al., 2004; Sugiura et al., 2001; Wu and Morahan, 1992).

Our results followed the results of several studies. Nieman et al. have reported that moderate-intensity aerobic exercise decreases the period and symptoms of infectious episodes among women with upper respiratory tract infection after brisk walking for 45 min, 5 days a week. (Nieman et al., 1990). Matthews et al. have demonstrated that moderate-vigorous-intensity aerobic exercise decreases the incidence and symptoms of upper respiratory tract infections in adult men and women (Matthews et al., 2002). A more recent study investigated the effect of moderate-intensity exercise on the development of cold symptoms among obese sedentary postmenopausal women who usually have reduced immune functions. They found that aerobic exercise significantly decreased the incidence of self-reported cold symptoms (Chubak et al., 2006).

In this study, Leucocytes showed a significant difference between groups as they increased significantly in the intervention group after two weeks of aerobic exercise. this might be attributed to that aerobic exercise elevates the recruitment of natural killers and T and B cells in the bloodstream. The neutral killers increase more than T cells, this leads to a decline in the CD3+: T cell percentage. This decline in CD3+: T cell percentage helps to increase the leukocyte recruitment process (Natale et al., 2003).

In this study, Lymphocytes showed a significant difference between groups with more increase in the intervention group after two weeks of aerobic exercise. Aerobic exercise causes an elevation in plasma catecholamines (dopamine, norepinephrine, and epinephrine) causing an increase in the serum lymphocytes. Epinephrine infusion induces mitogen-induced lymphocyte proliferation and lymphocyte apoptosis (Nieman and Nehlsen-Cannarella, 1994; Steensberg et al., 2001; Tvede et al., 1994). Moreover, salivary immunoglobulin-A showed a significant difference between groups as it increased in the intervention group after two weeks of aerobic exercise. This might be attributed to that the changes in the transport of IgA across the mucosal epithelium or sympathetically-mediated vasodilation in the oral submucosa and consequent elevation in the migration of cells synthesizing and secreting (Nieman and Nehlsen-Cannarella, 1994; Reid et al., 2001).

The findings of our study followed the results of Gonçalves et al. who have shown that 5-weeks of low-intensity aerobic exercise significantly increases the amounts of neutrophils in bronchoalveolar lavage fluid and tissue, pulmonary elasticity and resistance, TNF-alpha in lung tissue, protein leakage, plasma levels of IL-10 and IL-6, and IL 1beta, IL-6 and KC levels (Reis Gonçalves et al., 2012). Also, aerobic exercise can cause an increase in serum neutrophils, leukocytes, and monocyte, which can positively increase lung immunity against the COVID-19 virus. Lippi et al. have shown that a 21.1 km distance running increases the production of serum neutrophil, leukocyte, and monocyte in unprofessional runners (Lippi et al., 2010; Lippi et al., 2014). Lira et al. have demonstrated that an elevation in the levels of cytokine IL-6 and IL-10 occurs after 60-min of 5-km running (Lira et al., 2017). Li et al. have reported that circulating leukocytes, neutrophils, and monocytes increase after just one session of a prolonged moderate aerobic exercise (Li and Cheng, 2007).

In this study, there were non-significant differences between both groups after two weeks of intervention in interleukin-6, interleukin-10, and TNF-α. This might be attributed to that the participants in this study were non-regularly exercised individuals which have been demonstrated to have a usual lower serum Interleukin-10, -10, and TNF-α(Diao et al., 2020; Farhangimaleki et al., 2009; B. Pedersen, 1991). Besides, the participants performed a short-term exercise aerobic program (two weeks). Previous studies have reported that short-term aerobic exercise cannot induce significant differences in the levels of Interleukin-6, Interleukin-10, and TNF-α in sedentary individuals; while, long-term aerobic exercise can induce changes in these immune biomarkers (Balducci et al., 2010; Kadoglou et al., 2007; Viana et al., 2014). Arslan et al. reported that 12-weeks of moderate aerobic exercise could not induce any significant differences in TNF-α(Arslan et al., 2014). Martinis et al. reported that regular long-term aerobic exercise did not induce changes in the level of pro-inflammatory markers (Martins et al., 2009). Also, Moldoveanu et al. reported that short-term aerobic exercise could not induce changes in the pro-inflammatory markers (Moldoveanu et al., 2001).

The weaknesses of this study were that the researchers could not directly supervise the included patients during the exercise program due to the increased risk of infection that can occur for the researchers with direct contact with infected patients. Also, aerobic exercise was performed for two weeks only because this study aimed to investigate the short-term effect of aerobic exercise on patients with COVID-19 in the mild stage. This study did not investigate the difference in response between males and females to aerobic exercise. Future research should investigate the effect of long-term aerobic exercise on COVID-19 associated disorders and death rates and the response difference between genders and age groups to aerobic exercise.

7. Conclusion

The current study indicated that two -weeks of moderate-intensity aerobic exercise decreased the severity and progression of COVID-19 associated disorders and quality of life. Also, two weeks of aerobic exercise produced a positive effect on the immune system by increasing the amounts of Leucocytes, Lymphocytes, Immunoglobulin A.

8. Clinical application

This study can clinically help in improving the immune functions which can lead to a decrease in the cost of hospitalization. Also, this study helps to enhance the effectiveness of presented COVID-19 vaccines because of increased immune functions. Lastly, this study helps to decrease the suffering of COVID-19 patients by decreasing its associated disorders and mortality rates**.**

CRediT authorship contribution statement

Ayman A. Mohamed: Visualization, Investigation. **Motaz Alawna:** Conceptualization, Methodology, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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