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Original Article

Continuous versus low-intensity interval aerobic exercise in pulmonary rehabilitation after COVID-19

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ABSTRACT

Objectives: This study aimed to compare the effectiveness of mild-moderate intensity continuous training (CT) and low-intensity interval moderate-intensity training (LIIT) aerobic exercises in pulmonary rehabilitation after coronavirus disease 2019 (COVID-19).

Patients and methods: This prospective study was conducted between January 2021 and January 2022. Sixty-three patients (47 males, 16 females; mean age: 54.3±11.3 years; range, 25 to 81 years) with one or more residual symptoms following COVID-19 infections were randomly included in the CT (n=33) or LIIT (n=30) groups. Fifteen sessions (60 min, 3-5/week) of aerobic exercise (20-min 40% of peak workload for CT; 40% peak workload with 3-min loaded and 1-min nonloaded intervals for LIIT, with 5 min warm-up and cool-down), breathing, and upper extremity strengthening exercises were applied. Outcome measures were symptom-limited submaximal exercise test, and six-minute walk test (6MWT), the modified Medical Research Council (mMRC) dyspnea scale, modified Borg dyspnea scale, and Borg 6-20 rate of perceived exertion scale, hand grip strength, fat-free mass, Hospital Anxiety and Depression Scale (HADS), and 36-item Short-Form Health Survey.

Results: The maximum load and time reached during the exercise test, the 6MWT distance, hand grip strength, mMRC, HADS, and SF-36 scores significantly improved in both groups ($p<0.05$). Resting modified Borg dyspnea scores, heart rate, rate of perceived exertion, and oxygen supplementation requirement decreased significantly in the LIIT group ($p<0.05$). All posttreatment measures were similar in both groups ($p>0.05$). The changes in mMRC, resting heart rate, and 6MWT distance were significantly higher in the LIIT group compared to the CT group ($p<0.05$).

Conclusion: Both CT and LIIT improved functional capacity, dyspnea, tachycardia, depression, and quality of life measures safely and effectively in COVID-19 survivors with residual symptoms. Patients with poor clinical status who cannot tolerate CT after an acute pulmonary condition such as COVID-19 may benefit from LIIT.

Keywords: Aerobic exercise, COVID-19, dyspnea, long-COVID, post-COVID syndrome, pulmonary rehabilitation.

Coronavirus disease 2019 (COVID-19) is a multisystem disease with the most prominent effects on the pulmonary system. Many patients cannot be discharged home after the management of the infection due to an ongoing need for oxygen supplementation, persistent dyspnea, muscle weakness, fatigue, and an inability to walk as a result of deteriorated pulmonary function or decreased functional capacity.[1,2] Hospitalization for respiratory conditions is associated with clinical findings such as dyspnea, muscle deconditioning, decreased functional capacity, limitation in activities of daily living, and reduce quality of life (QoL).[3] These symptoms are similar to those observed in long COVID.[1,2] A previous study by Lau et al.,[4] which was conducted during the severe acute respiratory syndrome (SARS) epidemic due to the SARS coronavirus in 2003, indicated an improvement in 6-min walking distance and maximum oxygen consumption after a physical rehabilitation (PR) program consisting of aerobic and

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resistance exercises. Likewise, PR after COVID-19 has been reported to be indicated in patients with pulmonary function deterioration or accompanying symptoms.[5,6] Physical rehabilitation and exercise-based treatments have been reported to be beneficial after acute respiratory conditions. However, there is a wide range of variability in exercise type and intensity of proper exercises.[3,7-9]

Both intermittent aerobic and continuous aerobic exercise have been shown to equally improve the exercise capacity and the QoL in chronic obstructive pulmonary disease. Interval training is better tolerated than continuous aerobic exercise in chronic obstructive pulmonary disease due to dyspnea and muscle weakness in PR sessions due to captured air and dynamic hyperinflation.[10] Prescribing the optimal exercise intensity after acute conditions is of particular concern. Low-intensity exercise is recommended for COVID-19 survivors who require PR.[5] To our knowledge, no study in the literature has compared mild-moderate intensity continuous training (CT) and mild-moderate intensity low-intensity interval training (LIIT) as two types of aerobic exercise in PR of COVID-19 patients. This study hypothesized that *(i)* the highest intensity of aerobic exercise should be at the lower limit of mild-moderate intensity (40% of maximum) so as not to trigger hypoxia with excess effort and that *(ii)* LIIT may be an option to improve functional capacity in patients who cannot tolerate CT. Thus, this study aimed to compare the effectiveness of CT and LIIT in patients requiring PR after COVID-19 infection.

PATIENTS AND METHODS

This randomized prospective study was conducted on COVID-19 survivors referred for PR. The CONSORT reporting guideline was used.[11] The study was conducted at the cardiopulmonary rehabilitation laboratory of the Ankara Bilkent City Hospital, Physical Medicine and Rehabilitation Department, between January 2021 and January 2022. The patients recruited in the study were those who had completed treatment for a clinical diagnosis of COVID-19 infection and were then referred for a PR program with one or more of the findings of dyspnea, muscle weakness, decrease in walking distance, walking difficulty, an ongoing need for oxygen supplementation, and fatigue. Patients were excluded from the study if they had hemodynamic instability, limited cooperation, rheumatological disease, neurological disease, or unstable heart disease. After the assessment of the physiatrist, group allocations were made using the closed-envelope method. When the target patient number was reached, patient recruitment was terminated. The evaluation involved an initial total of 76 patients. The study was completed with a total of 63 patients (47 males, 16 females; mean age: 54.3±11.3 years; range, 25 to 81 years), with 33 patients in the CT group and 30 in the LIIT group. The study flowchart is shown in Figure 1. Written informed consent was obtained from all participants. The study protocol was approved by the Ankara City Hospital Ethics Committee (Date: 27.01.2021, No: E2-21-53). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All the assessments and treatment sessions were performed in the cardiopulmonary laboratory. After the initial assessments, patients were randomly assigned to the continuous mild-moderate intensity CT group or the LIIT group. All the patients wore surgical masks during the training sessions, which lasted 60 to 70 min. Due to the patient's access to the laboratory, sessions were applied three or five times a week, the frequency required for aerobic capacity gain. Exercise capacity was tested with a symptom-limited lower extremity ergometric test on a recumbent bicycle with an incremental program increasing 5 W/min (Ers.2 cardiac rehabilitation system; Ergoline, Bitz, Germany), with 12-lead electrocardiogram, pulse, blood pressure, and oxygen saturation (SpO_2) monitoring. The individual exercise protocols were performed in the Ers.2 cardiac rehabilitation system. The CT group received an intensity equal to 40% of the peak workload determined with the exercise test (5-min warm up, 20-min exercise, 5-min cool-down period), and perceived exertion was limited to 12 to 13 during the sessions. The LIIT group received an exercise intensity equal to 40% of the peak workload interrupted by active nonloaded intervals (3 min loaded, 1 min nonloaded), and perceived exertion was limited to 12 to 13 during the sessions. The duration of the aerobic exercise session was 40 min. The pulmonary rehabilitation program comprised 15 sessions, increasing the workload by 5 W per week. Gradual verticalization (sitting at bed, near bed, verticalization near bed, stepping in the room, and walking) was performed if needed for the patients at bed or wheelchair level. All the patients received breathing exercises (diaphragmatic breathing, air shifting, voluntary isocapnic hyperpnoea, and controlled coughing) if tolerated.

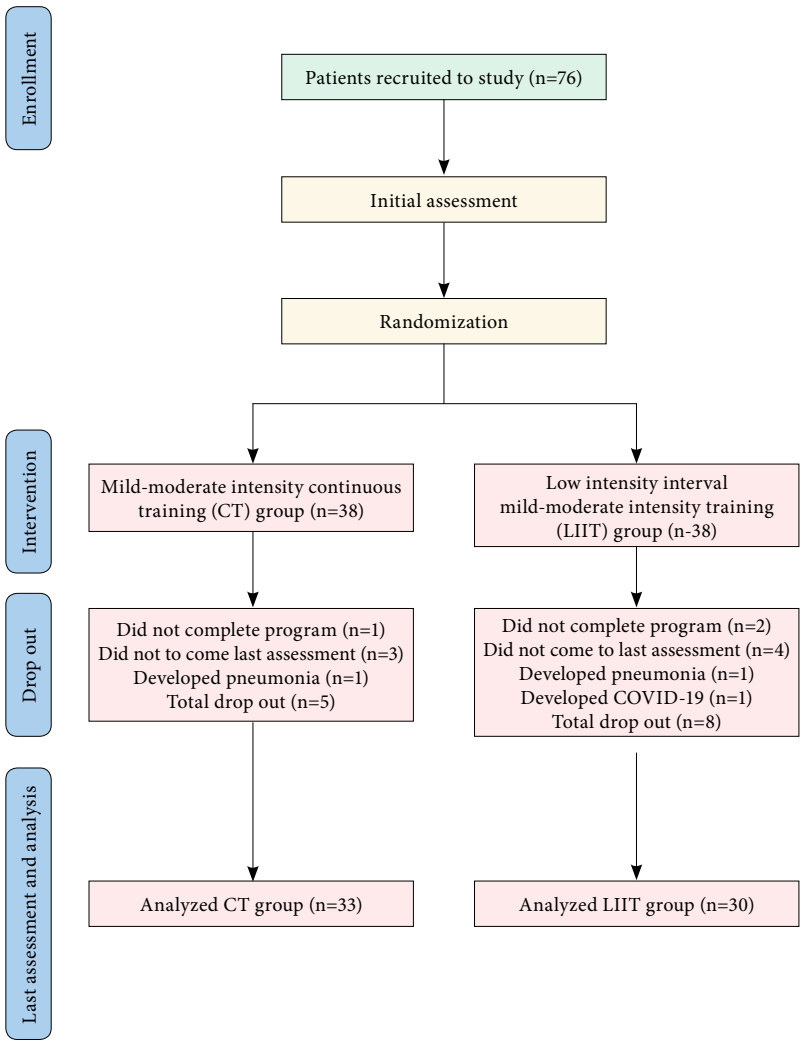

Figure 1. Flowchart of the trial.
COVID-19: Coronavirus disease 2019.

After two weeks, upper extremity and shoulder region strengthening exercises (15 min of 1 kg dumbbell exercises for three to four upper extremity muscles, 15 min of upper extremity ergometer) were added.

The patients who participated in the study were assessed before and after the program. The World Health Organization disease classification was used to classify patients according to the severity of the disease.[12] The functional capacity of the patients was tested by a physician and nurse using the six-minute walk test (6MWT) in a 30 m corridor, and recording the distance walked, pre- and posttest heart rate (HR), blood pressure, rate of perceived exertion (RPE), SpO_2, and the presence of oxygen requirement.[13] The modified Borg dyspnea (MBD) scale and the Borg 6-20 RPE scale were also used. The Borg 6-20 RPE scale, in which 6 represents no exertion and 20 represents extreme difficulty, is a subjective method to determine exercise intensity during assessments and training.[14,15] The modified Medical Research Council (mMRC) dyspnea scale tested physical activity levels related to dyspnea. This five-grade scale measures the physical activity level when a person feels dyspnea during daily physical activities.[16,17] Hand grip strength (HGS) was measured in the dominant extremity with a hand-held dynamometer (Baseline Hydraulic Hand dynamometer [90,718 kg]; Fabrication Enterprises Inc., White Plains, NY, USA). The measurements were taken with the patient sitting, shoulder adducted, neutrally rotated, elbow flexed to 90°

and supported from below, and the forearm in neutral rotation. The best of three measurements was used in the analysis. Fat-free mass was measured with a bioimpedance device (Tanita TBF-300M; Tanita Corporation, Tokyo, Japan). Hospital Anxiety and Depression Scale (HADS) was used to assess depression and anxiety symptoms of the patients. This scale consists of 14 items, seven assessing anxiety, and seven assessing depression symptoms. Total scores of 0 to 7 are accepted as normal, 8 to 10 as borderline, and ≥11 as abnormal.[18,19] Health-related QoL was assessed with the 36-item Short-Form Health Survey (SF-36), which evaluates eight areas: general health, physical function, mental health, bodily pain, physical role limitations, vitality, social function, and emotional role limitation. The scores were calculated and given as reported in the literature.[20]

Sample size calculation

In this study, the effect of CT compared to LIIT was investigated. The sample size required was calculated using G*Power version 3.0.10 software (Franz Faul, Universität Kiel, Kiel, Germany). The sample size was calculated as at least 68 participants (34 in each group), considering the change in functional capacity with a size effect of 0.40 and aiming to determine the difference between groups with a power of 90% and type 1 error of 5% with Student's t-test. The patient number was increased to 76 due to the possibility of dropout.

Statistical analysis

Data obtained in the study were analyzed statistically using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were given as mean ± standard deviation (SD) or median (min-max) values, and categorical data were given as frequency (n) and percentage (%). Normality analyses of continuous variables were assessed with the Kolmogorov-Smirnov goodness of fit test. Student's t-test was used in the analysis of variables that conformed to the normal distribution, and Mann-Whitney U test was used for those that did not. Before-after comparisons were performed using the paired samples t-test in dependent groups for data with normal distribution and the Wilcoxon signed-rank test was used to analyze nonnormally distributed data. Categorical variables were evaluated with the chi-square test or Fisher exact test in independent groups, and the McNemar test were used to compare dependent groups. A p-value <0.05 was considered statistically significant.

RESULTS

A statistically significant difference was determined between the groups concerning the World Health Organization COVID-19 disease severity classification (p=0.042).

The duration from COVID-19 infection until the initial assessment date was longer in the CT group (81±42.63 days) than in the LIIT group (57.73±37.36 days; p=0.025). The hospital length of stay due to COVID-19 infection was not different between the groups, whereas the length of intensive care unit (ICU) stay was significantly shorter in the CT group compared to the LIIT group (median of 0 and 7.5 days, respectively; p=0.007). The ratio of ICU stay was also higher in the LIIT group (70%) than in the CT group (30.3%; p=0.002). All the patients in the LIIT group (100%) received oxygen supplementation therapy during hospitalization, while this ratio was 84.8% in the CT group. In the CT group, patients received oxygen supplement therapy during active infection with a nasal cannula (33%), reservoir mask (24.2%), high flow (24.2%), or intubation (3%). These ratios were 10%, 30%, 40%, and 20% in the LIIT group, and the difference was significant (p=0.030). The requirement for oxygen supplementation during the first session of the PR program was 60% in the LIIT group and 15.2% in the CT group (p<0.001). From the SF-36 items, physical function (p=0.012), emotional role limitation (p=0.032), and social function (p=0.001) scores were lower in the LIIT group.

Age, sex, education level, number of medications, hemoglobin, hematocrit, platelet, white blood cell count, neutrophil ratio, blood glucose tests, resting blood pressure, SpO_2, the requirement for long-term oxygen therapy, and current steroid medication were not different between the groups, while creatinine levels were higher in the CT group, and alanine aminotransferase was higher in the LIIT group at the baseline assessments. Resting HR was significantly higher in the LIIT group compared to the CT group (99.1±17.43 bpm *vs.* 90.7±12.52 bpm; p=0.031). The distance in the 6MWT was shorter in the LIIT group than in the CT group (254.25±166.47 *vs.* 371.12±144.09; p=0.004). The results of the baseline assessments are summarized in Table 1.

In the CT group, after the PR program, exercise test duration and achieved maximum load increased significantly (p<0.001). Additionally, HGS increased (p=0.002), while the median mMRC level decreased significantly after PR (p<0.001).

TABLE 1
The comparison of general characteristics and initial physical examination findings between the groups (n=63)

	CT group (n:33)					LIIT group (n=30)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			53.5±11.6		37-78			55.1±11.1		25-81	0.560†
Sex											0.720*
Male	24	72.7				23	76.7				
Female	9	27.3				7	23.3				
Hospitalization for COVID-19	29	87.9				30	100.0				0.069**
Length of stay (day)			19.94±14.91					26.3±11.56			0.065†
ICU stay	10	30.3				21	70.0				**0.002***
Length of ICU stay (day)				0	0-35				7.5	0-30	**0.007‡**
Mild disease	1	3.0				0	0.0				**0.042***
Pneumonia	10	30.3				3	10.0				
Severe pneumonia	21	63.6				21	70.0				
Critical disease	1	3.0				6	20.0				
O_2 supplementation during hospital stay	28	84.8				30	100.0				**0.034****
O_2 supplementation type during hospital stay											**0.030***
NC	11	33.3				3	10.0				
RM	8	24.2				9	30.0				
HF	8	24.2				12	40.0				
I	1	3.0				6	20.0				
Time passed since event (day)			81±42.63					57.73±37.36			**0.025†**
O_2 supplementation need during rehabilitation	5	15.2				18	60.0				**<0.001***
Medication number			2.67±2.7					2.73±2.1			0.914†
BMI (kg/cm^2)			29.5±4.84					29.37±5.42			0.915†
FFM			59.88±10.54					58.66±7.91			0.607†
Resting systolic P			113.76±10.93					111.8±11.47			0.491†
Resting diastolic P			75.88±9.45					74.53±9.83			0.582†
HR			90.7±12.52					99.1±17.43			**0.031†**
mMRC				3	1-5				4	1-5	**0.005‡**
Resting MBD				0	0-2				0.5	0-3	0.172‡
Resting RPE				7	6-10				7	6-12	0.096‡
Hand grip strength			30.63±10.9					27.4±10.17			0.231†
Maximum load in exercise test (W)			34.39±24.07					25.5±16.37			0.089†
Maximum HR in exercise test (bpm)			113.7±13.33					115.27±17.8			0.692†
Maximum systolic BP in exercise (mmHg)			139.48±19.57					132.97±20.65			0.203†
Maximum diastolic BP in exercise (mmHg)			83.06±13.54					77.5±12.13			0.092†
Minimum SPO_2 (%)			92±4.08					90.23±3.79			0.081†
Maximum MBD in exercise				3	0-5				4	0.5-5	0.469‡
Exercise test duration (min)			9.88±4.7					8.1±3.5			0.096†
6 MWT distance (m)			371.12±144.09					254.25±166.47			0.004†
HADS anxiety			6.03±3.74					7.37±5.27			0.247†
HADS depression			5.64±3.92					7.1±5.47			0.232†
SF36 physical function			40.94±23.99					24.67±25.8			0.012†
SF36 physical role limitation			15.15±30.58					6.67±22.68			0.148†*
SF36 emotional role limitation			40.39±43.1					21.11±39.61			0.032‡
SF36 vitality			48.63±21.11					43.33±22.18			0.335†
SF36 mental health			64.61±19.21					64±24.59			0.913†
SF36 social function			33.56±28.72					12.9±21.14			0.001‡
SF36 bodily pain			54.98±26.76					44.42±31.48			0.155†
SF36 general health			49.55±19.7					43.5±20.81			0.241†

CT: Mild-moderate continuous training; LIIT: Low intensity interval mild-moderate intensity training; SD: Standard deviation; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; NC: Nasal cannula; RM: Reservoir mask; HF: High flow; I: Intubation; BMI: Body mass index; FFM: Fat-free mass; HR: Heart rate; mMRC: Modified Medical Research Council Dyspnea Scale; MBD: Modified Borg Dyspnea; RPE: Rate of perceived exertion; bpm: Beats per minute; BP: Blood pressure; 6 MWT: Six-minute walk test; HADS: Hospital anxiety depression scale; SF-36: 36-Item short form survey; W: watt: * Chi-square test; ** Fisher exact test; † Independent Samples t-test; ‡ Mann-Whitney U-test.

TABLE 2
The comparison of pre- and posttreatment variables in the CT group and the LIIITG (n=63)

	CT group (n=33)			LIIT group (n=30)		
	Pretreatment	Posttreatment	*p*	Pretreatment	Posttreatment	*p*
BMI (Mean±SD)	29.5±4.84	29.49±4.91	0.915†	29.37±5.42	29.91±4.98	**0.012†**
FFM (median [min-max])	59.88±10.54	60.43±11.78	0.155‡	58.66±7.91	58.29±11.02	0.147‡
Hand grip strength (median [min-max])	30.63±10.9	36.86±18.56	**0.002‡**	27.4±10.17	30.84±12.83	**0.005‡**
mMRC (median [min-max])	3 (1-5)	2 (1-4)	**<0.001****	4 (1-5)	2 (1-5)	**<0.001****
O_2 requirement n (%)	5 (%15.2)	3 (%9.1)	0.625***	18 (60.0)	2 (%6.7)	**<0.001[a]**
ET results						
Resting SPO_2 (Mean±SD)	95.24±2.81	96 (93-99)	0.076†	95.1±1.94	96 (92-98)	0.240†
Resting HR (Mean±SD)	89.55±12.81	87.21±14.04	0.313†	99.47±17.23	89.47±15.39	**<0.001†**
Resting BP (Mean±SD)	113.7±11.94/ 75.58±9.68	110.39±9.21/ 74.09±7.78	0.140†/ 0.301†	110.83±10.18/ 72.77±8.5	111.2±13.07/ 73.63±9.68	0.894†/ 0.701†
Resting RPE (Mean±SD)	7 (6-10)	6 (6-10)	0.397†	7 (6-12)	7 (6-11)	**0.031†**
Resting MBD (median [min-max])	0 (0-2)	0 (0-2)	0.051‡	0.5 (0-3)	0 (0-3)	**0.008‡**
Minimum SPO_2 (Mean±SD)	92±4.08	92.67±3.71	0.230†	90.23±3.79	91.07±2.95	0.188†
Max HR (Mean±SD)	113.7±13.33	115.64±14.83	0.314†	115.27±17.8	114.5±17.34	0.798†
Max BP mmHg systolic/diastolic (Mean±SD)	139.48±19.57/ 83.06±13.54	139.21±20.08/ 78.67±8.73	0.946†/ 0.070†	132.97±20.65/ 77.5±12.13	141.37±23/ 75.73±11.45	0.115†/ 0.517†
Max RPE (Mean±SD)	12.67±2.51	13.33±2.3	0.226†	12.6±3.1	12.4±2.44	0.768†
Max MBD (median [min-max])	3 (0-5)	2.95±1.26	0.713†	4 (0.5-5)	3.18±1.51	0.967†
Maximum load in exercise test (W) (Mean±SD)	34.39±24.07	54.39±19.64	**<0.001†**	25.5±16.37	52±24.8	**<0.001†**
Exercise test duration (min) (Mean±SD)	9.88±4.7	13.94±3.99	**<0.001†**	8.1±3.5	13.63±5.26	**<0.001†**
6 MWT results						
O_2 supplementation L/min	0 (0-6)	0 (0-1)	**0.039‡**	0.5 (0-5)	0 (0-2)	**0.001‡**
6^{th} min max HR	111,09±13,7	104,36±16,5	**0.013†**	109,87±20,54	105,5±20,24	0.165†
6^{th} min RPE	11.79±2.5	10.18±2.35	**0.004†**	11.17±2.84	10.37±2.43	**0.078†**
6^{th} min MBD	2 (0-5)	1 (0-4)	0.081†	3 (0-4)	1 (0-4)	**0.002†**
6^{th} min SPO_2	90.55±6.2	91.09±6.33	0.557†	88.57±5.09	91.23±4.57	**0.003†**
6 MWT distance (m) (Mean±SD)	371.12±144.09	426.76±134.98	**0.001†**	254.25±166.47	377.3±157.25	**<0.001†**
HADS anxiety (Mean±SD)	6.03±3.74	4.82±3.59	**0.017†**	7.37±5.27	5.73±4.82	**0.049†**
HADS depression (Mean±SD)	5.64±3.92	4.36±4.12	**0.049‡**	7.1±5.47	5±4.64	**0.020‡**
SF36 physical function (Mean±SD)	40.94±23.99	55.61±23.28	**0.001†**	24.67±25.8	51.83±23.83	**<0.001†**
SF36 physical role limitation (Mean±SD)	15.15±30.58	34.09±42.31	**0.025‡**	6.67±22.68	31.17±40.29	**0.003‡**
SF36 emotional role limitation (Mean±SD)	40.39±43.1	58.57±43.32	**0.018‡**	21.11±39.61	62.2±46.92	**<0.001‡**
SF36 vitality (Mean±SD)	48.63±21.11	57.27±21.47	**0.011†**	43.33±22.18	53.5±27.01	**0.037†**
SF36 mental health (Mean±SD)	64.61±19.21	72.73±18.48	**0.017†**	64±24.59	70.2±23.9	0.195†
SF36 social function (Mean±SD)	33.56±28.72	56.35±31.37	**<0.001†**	12.9±21.14	48.82±31.15	**<0.001†**
SF36 bodily pain (Mean±SD)	54.98±26.76	74.09±18.33	**<0.001†**	44.42±31.48	71.55±19.16	**<0.001†**
SF36 general health (Mean±SD)	49.55±19.7	59.85±16.08	**<0.001†**	43.5±20.81	53.83±20.91	**0.006†**

CT: Mild-moderate continuous training; LIIT: Low intensity interval mild-moderate intensity training; SD: Standard deviation; BMI: Body mass index; FFM: Fat-free mass; mMRC: Modified Medical Research Council Dyspnea Scale; ET: Submaximal exercise test; HR: Heart rate; BP: Blood pressure; RPE: Rate of perceived exertion; MBD: Modified Borg Dyspnea; 6 MWT: Six-minute walk test; HADS: Hospital anxiety depression scale; SF-36: 36-Item short form survey; W: watt; * Independent Samples t-test; ** Mann-Whitney U-test; † Paired Samples t test; ‡ Wilcoxon Signed Rank test; [a] McNemar Test bStatistical comparison of post treatment values of CT and LIIT group p<0.05 (none of the variables were different).

In the 6MWT, walking distance increased significantly after PR (426.76±134.98 m) compared to before (371.12±144.09 m; p=0.001), while the 6-min RPE (p=0.004), maximum HR (p=0.013), and the requirement of liters oxygen of per minute (p=0.039) decreased significantly after PR (Table 2).

When we performed the comparison of pre- and posttreatment values in the LIIT group, maximum load (p<0.001) and exercise time (p<0.001) increased, while RPE decreased (p=0.031) significantly in the symptom-limited incremental lower extremity ergometric exercise test. A statistically significant increase was determined in weight (p=0.010), body mass index (p=0.012), and HGS (p=0.005), while the median mMRC level decreased (p<0.001). In the 6MWT, resting MBD (p=0.002), 6-min MBD (p=0.002), SpO_2 (p=0.003), the requirement of liters of oxygen per minute (p=0.001), and the rate of desaturation (p=0.004) decreased significantly after PR (p<0.001). Total walking distance significantly increased (from 254.25±166.47 to 377.3±157.25; p<0.001) after the PR program (Table 2).

The ratio of patients with oxygen supplementation requirements was higher in the LIIT group (60%) than in the CT group (15.2%) at baseline. After the PR program, the requirement for oxygen supplementation decreased significantly to 6.7% in the LIIT group (p<0.001) and to 9.1% in the CT group, with no significant difference remaining between the two groups (p=0.546). In both groups, HADS scores and nearly all SF-36 dimensions improved significantly after the PR program (p<0.05; Table 2). When we compared the posttreatment outcome measures, there was no statistically significant difference between the groups (p>0.05).

TABLE 3
The comparison of the changes from pre- to posttreatment in the CT and LIIT group (n=63)

	CT group (n=33)			LIIT group (n=30)			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
BMI	−0.02±1.21			0.54±1.11			0.060*
FFM		0.71	−8.81-6.61		0.93	−42.34-7.09	0.700**
Hand grip		4.7	−13.7-84		2.15	−11-36.3	0.342**
mMRC		−1	−3-0		−2	−4-1	**0.032****
Resting SPO_2	0.76±2.37			0.47±2.13			0.612*
Resting HR (bpm)	−2.33±13.07			−10±13.64			**0.026***
Resting RPE	−0.24±1.62			−0.9±2.17			0.176*
Resting MBD		0	−2-1		−0.5	−2.5-1	0.135**
Maximum load in exercise test (W)	20±18.03			26.5±22.29			0.206*
Max RPE	0.67±3.09			−0.2±3.68			0.315*
Exercise test duration (min)	4.06±3.61			5.53±4.76			0.169*
6MWT distance (m)	55.64±84.3			123.05±114.75			**0.010***
HADS anxiety	−1.21±2.77			−1.63±4.35			0.645*
HADS depression		0	−10-5		−1	−11-7	0.372**
SF36 physical function	14.67±21.79			27.17±27.72			0.050*
SF36 physical role limitation	18.94±45.51			24.5±36.89			0.472**
SF36 emotional role limitation	18.18±43.37			41.09±47.68			0.089**
SF36 vitality	8.64±18.34			10.17±25.48			0.784*
SF36 mental health	8.12±18.51			6.2±25.58			0.732*
SF36 social function	22.79±30.09			35.9±32.39			0.101*
SF36 bodily pain	19.11±22.29			27.13±31.24			0.242*
SF36 general health	10.3±12.8			10.33±18.89			0.994*

CT: Mild-moderate continuous training; LIIT: Low intensity interval mild-moderate intensity training; SD: Standard deviation; BMI: Body mass index; FFM: Fat-free mass; mMRC: Modified Medical Research Council Dyspnea Scale; bpm: Beats per minute; HR: Heart rate; RPE: Rate of perceived exertion; mMRC: Modified Medical Research Council Dyspnea Scale; MBD: Modified Borg Dyspnea; 6MWT: Six-minute walk test; HADS: Hospital anxiety depression scale; SF-36: 36-Item short form survey; W: watt; * Independent Samples t-test; ** Mann-Whitney U-test.

A between-group analysis assessed the beneficial effect of two aerobic exercise protocols. The change from before to after treatment was examined with delta values, and the improvement in mMRC (p=0.032), decrease in resting HR (p=0.026), and increase in 6MWT (p=0.010) were determined to be greater in the LIIT group. The other parameters showed no significant difference. The comparisons of the delta values are given in Table 3.

DISCUSSION

This study demonstrated that both mild-moderate CT and mild-moderate aerobic training with low-intensity intervals are effective protocols and improve functional capacity, dyspnea, tachycardia, QoL, depression, and anxiety in patients with COVID-19 (pneumonia, severe pneumonia, and critical disease survivors) with residual symptoms. Although the posttreatment outcome measures were similar between the groups, the increase in the distance achieved in the 6MWT, the improvement in physical function level related to dyspnea (mMRC), and the decrease in resting HR was greater in the LIIT group than in the CT group. This may have been the result of the initial difference between the groups. When the initial status of the patients was compared, the disease severity was higher, the time passed since diagnosis and the 6MWT distance was shorter, the ICU length of stay was longer, and the need for oxygen supplementation in the first session was greater in the LIIT group than in the CT group. Thus, the patients in the LIIT group group started from a weaker position but caught up with the CT group by the end of the PR program. Therefore, the results of the current study may offer a route for PR of patients with a poor clinical status after an acute severe pulmonary attack, such as exacerbations.

There are limited clinical studies on exercise-based treatments after COVID-19 in the literature. Rayegani et al.[21] evaluated a two-week exercise-based PR program on 35 patients discharged from the ICU after severe COVID-19. Similar to the current study, the mean SpO_2 increased, mean HR and dyspnea severity decreased, and there were improvements in QoL measures after the PR program. Unlike the current study, the patients had a shorter disease duration; the program did not include aerobic exercise and consisted of callisthenic and respiratory exercises (60 min, two sessions/week), supervised for one week.[21] Our study offers an advantage by objectively assessing the functional capacity and demonstrating the effectiveness and safety of aerobic exercises under continous monitoring of SpO_2, blood pressure, and electrocardiogram in patients with long COVID. Nevertheless, both studies support the benefits of an exercise program after COVID-19.

Nopp et al.[22] evaluated 58 outpatients (nearly half with mild to moderate disease) who survived COVID-19 with residual symptoms. Following a six-week program consisting of endurance training, respiratory exercises, and strengthening exercises, improvement in 6MWT, MDB level, fatigue, functional levels, and pulmonary function test results were reported.[22] The current study differed from Nopp et al.'s[22] study with a population that mostly recruited patients with a severe disease history and the requirement of oxygen supplementation during initial training. Our study approved the safety and effectiveness of aerobic exercise with CT and LIIT methods. In addition, we showed that LIIT may be an option for patients with poor clinical status who mostly require oxygen supplementation.

Nambi et al.[23] included male patients aged 60 to 80 years with sarcopenia and post-COVID-19 symptoms. Comparisons were made of low (40 to 60% HR maximum) and high-intensity aerobic exercise (60 to 80% HR maximum) in addition to strengthening exercises, and the intensity was determined with target HR ratios. In their study, patients with obvious muscle mass loss and handgrip <24 kg were excluded; the exercise duration was 20 min of treadmill and 10 min of cycle ergometer, followed by 15 min of resistance training with warm-up and cool-down periods. Better results (kinesiophobia, QoL, and HGS) were determined in the low-intensity aerobic exercise group.[23] The high-intensity group might not have achieved the maximum HR during the whole session due to inadequate muscle reserve, so these patients might not have been able to meet the requirements of aerobic exercise to gain benefits. The maximum HR method also has some disadvantages in maintaining the steady state of HR during the whole session. Kinesiophobia may be negatively related to unachievable exercise sessions. The current study included male and female patients who were individually prescribed exercise intensity using an ergometer test. At the end of the program,

both interventions improved outcome measures. Our study also found that good results may be achieved by prescribing the exercise intensity individually without putting the patients at risk of high-intensity exercise, which may increase the depth of hypoxia and degree of tachycardia, which would prevent the completion of the aerobic exercise sessions,[24] and this is also valid for patients with COVID-19. Patients with a worse initial clinical status could also be able to perform a PR program and obtain benefits with LIIT successfully. Low-intensity interval aerobic exercise programs may be a method for patients after an acute exacerbation such as COVID-19 pulmonary involvement.

Rao et al.[25] reported improvements in cough score, SpO_2, and 6MWT in the retrospective data of patients with long COVID who received PR consisting of breathing exercises and airway cleaning strategies. The current study differed from that study in terms of the aerobic exercise component. In their study, 14% of the patients were discharged with oxygen supplementation therapy, while in our study, this rate was only 9.1% in the CT group and 6.7% in the LIIT group. Endurance exercise is one of the essential parts of PR.[24] The benefit of aerobic exercise may be the reason for our better results.

The current study supports the need for aerobic exercise among COVID-19 survivors. It has been shown that peripheral muscle capillarization is associated with aerobic capacity.[26] In a study of COVID-19 survivors who had recovered from critical illness, follow-up cardiopulmonary exercise tests showed that resting metabolic rate increased, and limitations in exercise were especially a result of a hypermetabolic state and impaired oxygen utilization.[27]

This study had some limitations. The methodology of this study did not exclude the expected positive effect of time passed after infection, and a control group was lacking. Nevertheless, all the patients recruited in the study had residual symptoms that did not resolve spontaneously. Furthermore, due to ethical issues, none of the patients were followed without treatment. Bedside mobilization exercises were performed in addition to the PR program for patients who could not walk independently, as this is a necessity for patients with lung disease to achieve the physical activity level required to manage activities of daily living. However, this study can be considered of high quality, as the patients were monitored and supervised closely during the exercise sessions, ensuring the proper implementation of the exercise intensity.

In conclusion, for patients with residual symptoms after COVID-19, a PR program of CT or LIIT improves functional capacity, dyspnea, tachycardia, QoL, depression, and anxiety. Both protocols can be preferred for patients who cannot return to activities of daily living as a result of an acute pulmonary event or exacerbation, such as COVID-19. Low-intensity interval aerobic training may be a good option for patients with poor functional capacity.

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