FACTORS AFFECTING MEDIUM-TERM AEROBIC CAPACITY IN COVID-19 PATIENTS

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ABSTRACT

Introduction*: To evaluate PCR-positive COVID-19 patients' aerobic capacities during the active disease period and in the 3rd month after treatment and determine the demographic and disease characteristics associated with it.*

Materials and methods*: The study is a prospective, cross-sectional analysis conducted on 123 PCR positive inpatients. The study involved a total of 99 patients who completed follow up. Patients' demographic and disease characteristics, Nord -Trøndelag Health Study Physical Activity Level for Work (HUNT), were compared in terms of aerobic capacity (6-minute walking test) at treatment onset and third month and the change between these two measurements. In addition, demographic and disease characteristics of patients were grouped according to age (18-29, 30-59, 60-64 and >65 years), gender, BMI (<18.5%, 18.5%-24.9% and overweight ≥25%), comorbidities, smoking, level of work physical activity (sedentary, mild, moderate and severe) duration of hospital treatment, presence of pneumonia and oxygen requirement, and compared in terms of aerobic capacity at treatment onset and third month and the change between these two measurements.*

Results*: Older age (r:-0.573, p=0.001 and r:-0.488, p=0.001, respectively), the presence (r:-0.322, p=0.001 and r:-0.238, p=0.017, respectively) and number of comorbidities (r:-0.367, p=0.001 and r:-0.257, p=0.010, respectively), oxygen requirement (r:-0.510, p=0.001 and r:-0.439, p=0.001, respectively), and pneumonia presence (r:-0.693, p=0.001 and r:-0.607, p=0.001, respectively) were negatively correlated with aerobic capacity at treatment onset and third month, and positively correlated with smoking (r:0.385, p=0.001 and r:0.416, p=0.001, respectively) and physical activity level (r:0.698, p=0.001 and r:0.624, p=0.001, respectively). The patients with heavy physical activity had significantly higher aerobic capacity than other levels.*

Conclusion*: The higher aerobic capacity and aerobic capacity change may be correlated with the higher work activity level before the illness. Continuing physical activity, even at home, will promote recovery after the illness.*

Keywords: *COVID-19, aerobic capacity, 6-minute walking test, work-related physical activity.*

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Introduction

Coronavirus disease 19 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which continues to spread throughout the World[(1)]. COVID-19 may cause mild disease but can progress to severe pneumonia and may end with acute respiratory distress syndrome, septic shock and, multiple organ failure[(2)]. As can be seen from these findings, the primary and severe effect of COVID-19 is on the lungs. One can predict that this situation will affect the level of patients' physical activities. Studies have shown that aerobic capacities are involved even in young, PCR-positive asymptomatic patients[(3)]. Physical activity has improving and protective effects on cardiovascular, pulmonary, musculoskeletal, neurological, endocrine, and immune systems. Studies have reported that the risk of death increases by 20-30%, generally due to physical inactivity and decreased

activity[4]. Mortality risk increases even more with comorbidities and physiological changes such as changes in the musculoskeletal system, loss of elasticity and, neurological degeneration in the elderly, causing severe lung infection[5].

Thus, the treatment of active disease is not enough. Secondary consequences of the disease, such as a decrease in physical activity, increase morbidity, and mortality. Therefore, we think it is invaluable to know the factors that reduce aerobic capacity, known as secondary complications. There is no study investigating the patients and disease-related factors affecting both short-term and medium-term aerobic capacity.

Therefore, in the present study, it was aimed to evaluate the aerobic capacities of PCR-positive COVID-19 patients during the active disease period and in the 3rd month after treatment and determine the demographic and disease characteristics associated with it.

Material and method

The present study was a prospective and cross-sectional analysis conducted on 123 PCR positive patients hospitalized in our COVID-19 clinic between June and November 2020. Twenty-four patients were excluded because they lost to follow-up. The study was completed with 99 patients. Before the evaluation, the patients were given verbal and written information on the nature of the study. Informed consent forms were signed upon admission to the trial. All procedures were conducted according to the relevant principles of the Helsinki Declaration. Moreover, approval of the study was obtained from both the national and local Ethics Committees (Approval ID E1-20-1121).

Patients

There was no quarantine in the country during the study period, and each PCR positive patient was hospitalized until their tests were negative and their symptoms were resolved.

Inclusion criteria were; patients over 18 years of age, who were not bedridden, not on a mechanical ventilator, cognitively intact cooperative and, ambulatory with or without support were included in the study.

Exclusion criteria were; patients with a mechanical ventilator, being bedridden or wheelchair dependent, unable to cooperate, with known progressive/non-progressive neurological disease, patients with previously diagnosed pulmonary disease, previous surgery and a trauma history of the lower extremities and vertebrae, as well as those with a history of malignancy and inflammatory disease were not included in the study.

Patients' Demographic and Disease Characteristics

The patients' demographic characteristics, including age, gender, body mass index (BMI), presence of comorbidity, smoking status, and work, were questioned.

In order to investigate the detailed effect of demographic characteristics on the aerobic capacity of the patients; age range was selected as 18-29, 30-59, 60-64 and, > 65 (6), BMI was categorized as underweight (<18.5), normal (18.5-24.9) and overweight(≥25).

Comorbidities were grouped as one additional comorbidity, two additional comorbidities, ≥three comorbidities, smoking status as smoking, non-smoking, and quitting (patient not smoking for at least five years). Work status was classified according to work-related physical activity levels using the Nord -Trøndelag Health Study Physical Activity Level for Work (HUNT)[7].

This scale scores physical activity level at work. According to this, patients were grouped according to their work status and physical activity level. The categories were defined as; Level 1: sedentary workers, Level 2: mild-activity workers (work involving walking but no heavy lifting), Level 3: moderate-activity workers (work predominantly involving walking), and Level 4: severe-activity workers (work involving heavy lifting and especially tasks requiring strenuous physical activity).

Disease characteristics, including the duration of the patients' hospital stay for treatment, the drugs used, the presence of pneumonia, and the oxygen requirement, were recorded. The treatment duration was grouped as first 10 days and 11-14 days, and the drugs used were grouped as 1 drug, 2 drugs, and 3 drugs. For the presence of pneumonia, pulmonary CT was performed on the same day as the evaluation.

Aerobic capacity measurement

The 6-minute walking test (6MWT) was performed to assess the patients' current aerobic capacity when vital signs were normal. For the 6-minute walking test, a 30- meter distance was measured and marked. After the patient had 2 trial walks and rested for 30 minutes, the longest distance he had walked

was recorded in meters. 6MWT was applied to all patients on the first day of hospitalization and in the 3rd month.

Study protocol

Demographic and disease characteristics of patients were grouped according to age, gender, BMI, presence, and the number of comorbidities, smoking status, level of work physical activity, duration of hospital treatment, presence of pneumonia and oxygen requirement, and compared in terms of aerobic capacity at treatment onset and third month and the change between these two measurements. Later, demographic and disease characteristics were correlated with the change in aerobic capacity and aerobic capacity at treatment onset and third month.

Statistical analysis

Data analyses were made using the Statistical Package for the Social Sciences (SPSS) 22.0 for Windows. The continuous variables were evaluated with the Kolmorow-Smirnow test as to whether or not they were different from the normal distribution. Descriptive statistics were shown as mean ± standard deviation (SD) and median (minimum-maximum) for continuous variables and frequencies and percentages (%) for nominal variables. The treatment onset and third-month 6MWT measurements were compared with the Wilcoxon test. The treatment onset and third month aerobic capacity of the patients and the change in 3 months were evaluated by Student t-test and Mann-Whitney U tests for paired groups, ANOVA and Kruskal-Wallis tests for more than two groups according to demographic and disease characteristics. For the nominal variables, χ^2 and Fisher's exact tests were used in the intergroup comparison. Point biserial and Pearson's correlation coefficients were used to establish the relationship between aerobic capacity at treatment onset, third, and the change in third month, and demographic and disease characteristics. The statistical significance level was set at $p < 0.05$.

Results

The mean age of 99 patients included in the study was 49.06 ± 14.51 years, 66 (51.6%) were female, and 62 (48.4) were male. 41 (41.4%) of the patients had comorbidity, 22 of them (22.2%) had HT, 17 (17.2%) had DM, 9 (21.9%) had CAD and 5 (5.1%) had COPD. The demographic and disease characteristics of the patients are presented in Tables 1 and 2. Twelve (12.1%) of the patients had oxygen requirement, 41 (41.4%) had pneumonia, and aerobic capacity was significantly increased in the 3rd month compared to the beginning of the treatment ($p = 0.001$).

	n=99
Age (year) *mean±SD*	49.06±14.51
18-29 n(%)	10 (10.1)
30-59 n(%)	27 (27.3)
60-64 n(%)	48 (48.5)
>65 n(%)	14 (14.1)
Gender n(%)	
Female	46 (46.5)
Male	53 (53.5)
BMI (%) *mean±SD*	27.91±4.44
Underweight (<18.5) n(%)	0
Normal (18.5-24.9) n(%)	20 (20.2)
Overweight (>25) n(%)	79 (79.8)
Comorbidity n(%)	41 (41.4)
Number of comorbidity n(%)	
1	25 (25.3)
2	12 (12.1)
3	4 (4.0)
Smoking n(%)	
Yes	19 (19.2)
No	71 (71.7)
Quitted	9 (9.1)
Work related physical activity n(%)	
Sedantary job	37 (37.4)
Work involving walking, no heavy lifting	41 (41.4)
Work involving walking and heavy lifting	16 (16.2)
Strenuous physical work	5 (5.0)

Table 1: Demographic characteristics.
SD: Standard deviation, BMI: body mass index.

The distribution and comparison of aerobic capacity measurements at treatment onset and third month and the change in 3 months according to demographic and disease characteristics are presented in Tables 3 and 4. Aerobic capacity at treatment onset (for all $p = 0.001$) and third month (for all $p = 0.001$), and the change in aerobic capacity with treatment at third-month ($p = 0.011$, $p = 0.017$, $p = 0.021$, respectively) were significantly lower in patients over 65 years of age compared to all other age groups (18-29, 30-59, and 60-64).

There was a significant difference between no comorbidity and having 2 or 3 comorbidities in the first measurement ($p = 0.048$, $p = 0.029$, respectively). There was a significant difference between no comorbidity and 3 comorbidities in the 3rd-month measurement ($p = 0.032$). Also, there was a significant difference between no comorbidity

and 2 or 3 comorbidities with the aerobic capacity change in 3 months (p = 0.027, p = 0.019).

	n=99
Length of stay (days) *median (min-max)*	4.0 (1.0-14.0)
<10 days	93 (93.9)
11-14 days	6 (6.1)
Treatment *n(%)*	
HCQ	99 (100)
CLX	99 (100)
AZT	18 (18.2)
FVP	3 (3.0)
MOK	1 (1.0)
The number of drugs n(%)	
1 drug	0
2 drugs	77 (77.8)
3 drugs	22 (22.2)
Need for oxygen treatment *n(%)*	12 (12.1)
Pneumonia n(%)	41 (41.4)
6MWT at the onset of treatment (meter) *median (min-max)*	440.00 (60.0-1000.80)
6MWT in 3rd month (meter) *median (min-max)*	518.50 (110.0-1116.00)

Table 2: Disease characteristics.
Min-max: minimum-maximum, HCQ: hydroxychloroquine, CLX: clexane, AZT: azithromycin, FVP: favipiravir, MOK: moxifloxacin, 6MWT: 6-minute walking test.

There was a significant decrease in aerobic capacity at treatment onset, third month and in the aerobic capacity change in 3 months in patients who smoking compared to patients who quit smoking (p = 0.001, p = 0.001, p = 0.018, respectively) or who don't smoking (p = 0.002, p = 0.001, p = 0.025).

Sedentary worker patients had low aerobic capacity at treatment onset and third month compared to patients with mild, moderate, and heavy work activity (p = 0.001 for all). Patients with heavy physical activity had higher aerobic capacity compared to patients with sedentary (p = 0.001, p = 0.001), mild (p = 0.001, p = 0.003) and moderate (p = 0.001, p = 0.007) physical activity at treatment onset and third month. There was no difference in the change of aerobic capacity in patients with different work-related physical activity levels.

The aerobic capacity of the patients who used 2 drugs for COVID-19 was higher than those who used 3 drugs at treatment onset and third month (p = 0.004, p = 0.004). The treatment onset and third month aerobic capacity was significantly lower in patients with a long hospital stay (p = 0.024, p = 0.017), oxygen requirement (p = 0.001, p = 0.001), and presence of pneumonia (p = 0.001, p = 0.001) but the change in aerobic capacity was not different between groups.

The correlation analysis of the aerobic capacity at treatment onset and third month and the aerobic capacity change in 3 months with the demographic and disease characteristics is presented in Table 5. In correlation analysis, the treatment onset and third month aerobic capacity levels were found to be negatively associated with increased age, comorbidity, the number of comorbidities, oxygen requirement, and the presence of pneumonia, and positively associated with smoking increased physical activity levels.

Discussion

As a result of the study, it was found that age increase, the presence and number of comorbidities, oxygen requirement, and pneumonia presence were negatively correlated with aerobic capacity at treatment onset and third month and positively correlated with smoking and strenuous physical activity. On the other hand, no parameters were effective on the aerobic capacity change in the 3 months.

COVID-19 is a novel enveloped RNA beta-coronavirus, and it is known as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (8). As it causes respiratory failure, the disease is closely related to aerobic capacity and physical activity. Studies have shown that aerobic capacity increases lung functions and prevents lung damage (9-13). Aerobic capacity is increased by restoring normal lung tissue elasticity and increasing respiratory muscle strength and endurance, which help in increasing the ventilation, lung mechanics, and decreasing lung damage. In cases where aerobic capacity is reduced, healing processes are also negatively affected.

Aerobic capacity decreases with age-related changes in elderly patients. Because with aging, the lung volume and capacity, the maximum heart rate and maximum cardiac output decrease, and muscle mass loss occur due to motor neuron loss (5,14). As a result of the reversal of the healing process, these progressive losses cause a decrease in capacity. In our study, due to the effects of aging, aerobic capacity in the pre-treatment period and third month and aerobic capacity change in 3 months were lower in patients over 65 years compared to those of other age groups, and being over 65 years of age negatively affected aerobic capacity.

Functional aerobic capacity represents the maximum oxygen consumption rate due to muscle contractions and is considered the gold standard measurement for the cardiorespiratory system's functional limit[15].

This means that the conditions affecting the cardiopulmonary system also affect aerobic capacity. In studies investigating risk factors for COVID-19 disease, it was found that advanced age, the presence of additional comorbidity, and smoking were associated with disease severity[16-19].

In all these meta-analyses, the association of smoking with severe illness and high mortality has been reported. In our study, smoking was considered as a separate parameter, but we know that these smokers may be younger and have less comorbidity than those who quit or do not smoke.

	Treatment onset 6MWT Median (min-max)	**p**	**3rd month 6MWT Median (min-max)**	**p**	**Change during 3 months Median (min-max)**	**p**
Age (year)						
18-29	530.0 (428.0-728.0)		626.0 (462.0-785.0)		76.60 (34.0-148.0)	
30-59	468.0 (120.6-840.0)		567.20 (193.0-885.0)		68.00 (-38.0-226.0)	
60-64	447.0 (98.0-10008.0)	**0.001**	512.55 (142.0-1116.0)	**0.001**	61.25 (-73.0-211.0)	**0.029**
>65	120.0 (60.0-234.0)		192.50 (110.0-786.0)		40.20 (-25.0-724.0)	
Gender						
Female	437.0 (66.0-734.0)	0.641	502.05 (110.0-786.0)	0.627	57.10 (-38.0-720.0)	0.938
Male	440.0 (60.0-1000.8)		524.10 (140.0-1116.0)		62.00 (-73.0-724.0)	
BMI (%)						
Normal (18.5-24.9)	460.0 (78.0-840.0)	0.518	521.0 (140.0-885.0)	0.578	61.10 (32.0-224.0)	0.908
Overweight (>25)	440.0 (60.0-1000.8)		511.10 (110.0-1116.0)		54.00 (-73.0-724.0)	
Comorbidity n(%)						
0	500.50 (114.0-840.0)		560.80 (148.0-885.0)		55.05 (-73.0-226.0)	
1	384.0 (98.0-1000.8)		485.0 (110.0-1116.0)		54.00 (-22.0-211.0)	
2	296.0 (60.0-704.0)	**0.003**	361.50 (140.0-824.70)	**0.032**	48.60 (-25.0-724.0)	**0.030**
3	220.5 (80.0-324.0)		254.0 (110.0-422.0)		34.50 (28.0-98.0)	
Smoking n(%)						
Yes	514.0 (120.6-1000.8)		647.0 (193.0-1116.0)		82.20 (-31.9-226.0)	
No	448.0 (60.0-728.0)	**0.001**	526.1 (110.0-824.0)	**0.001**	57.20 (-73.0-724.0)	**0.027**
Quitted	214.0 (108.0-224.0)		244.0 (142.0-422.0)		30.00 (8.0-98.0)	
Physical activity level						
Sedanter	212.0 (60.0-562.8)		264.0 (110.0-786.0)		57.00 (-25.0-724.0)	
Mild-activity	497.0 (120.6-728.0)		564.40 (160.0-785.0)		57.65 (-31.9-226.0)	
Moderate activity	506.0 (210.0-734.0)	**0.001**	592.0 (264.0-766.0)	**0.001**	54.00 (-73.0-211.0)	0.214
Severe-activity	718.0 (630.0-1000.8)		854.0 (647.0-1116.0)		65.20 (17.0-136.0)	

Table 3: Distribution and comparison of aerobic capacity at treatment onset, third month and aerobic capacity change by demographic characteristics.
BMI; body mass index, 6MWT; 6-minute walking test.

In our study, the presence of comorbidity and especially 3 or more comorbidities may have caused both a decrease in the measurement scores of aerobic capacity and less improvement in aerobic capacity. An exciting result of our study; while aerobic capacities and recovery status were lower in those who quit smoking than those who smoke and never smoked, there was a positive correlation between smoking and aerobic capacity levels. COVID-19 and smoking have taken place in many studies and meta-analysis in the literature as a controversial situation due to the relationship of COVID-19 with ACE receptors[20-21].

Likewise, those who quit smoking may have been older patients with high additional comorbidity. So we think that evaluating smoking as a separate parameter may not be correct; it should be evaluated concerning other demographic characteristics.

Another interesting result of our study is that those who have a sedentary job had lower aerobic capacity measurements than those with other physical activity levels, and those who have heavy physical activity had significantly higher aerobic capacity than other levels.

Considering that the most serious effects of COVID-19 are via the pulmonary system, a

more severe course will be expected in a patient with physical inactivity as it has been shown that physical inactivity and sedentary lifestyle affect lung functions and reduce aerobic capacity even in healthy people without lung disease[5].

	Treatment onset 6MWT Median (min-max)	p	3rd month 6MWT Median (min-max)	p	Change during 3 months Median (min-max)	p
LOS						
<10 days	448.0 (60.0-1000.8)	**0.024**	526.1 (110.0-1116.0)	**0.017**	58.10 (-73.0-724.0)	0.235
11-14 days	132.0 (114.0-530.4)		196.0 (148.0-568.0)		43.80 (28.0-124.0)	
The number of drugs						
2 drugs	468.0 (60.0-1000.8)	**0.004**	560. 0 (110.0-1116.0)	**0.004**	59.20 (-73.0-724.0)	0.512
3 drugs	241.4 (78.0-702.0)		291.0 (110.0-684.0)		51.25 (-22.0-206.0)	
Oxygen requirement						
Yes	116.5 (66.0-324.0)	**0.001**	176.5 (110.0-786.0)	**0.001**	52.90 (-25.0-720.0)	0.373
No	468.0 (60.0-1000.8)		558.0 (110.0-1116.0)		57.20 (-73.0-724.0)	
Pneumonia						
Yes	521.0 (203.0-1000.8)	**0.001**	588.0 (242.0-1116.0)	**0.001**	58.65 (-73.0-224.0)	0.375
No	210.0 (60.0-704.0)		264.0 (110.0-824.0)		52.0 (-25.0-724.0)	

Table 4: Distribution and comparison of treatment onset, third month aerobic capacity and aerobic capacity change according to their demographic characteristics.
LOS; length of stay, 6MWT; 6-minute walking test.

	Treatment onset 6MWT r/p	3rd month 6MWT r/p	Change during 3 months r/p
Age	**-0.573/0.001**	**-0.488/0.001**	0.112/0.271
Male Gender	0.047/0.641	0.049/0.627	0.008/0.937
BMI	-0.140/0.168	-0.154/0.128	-0.039/0.701
Comorbidity	**-0.322/0.001**	**-0.238/0.017**	-0.131/0.196
Number of comorbidity	**-0.367/0.001**	**-0.257/0.010**	0.176/0.081
Smoking	**0.385/0.001**	**0.416/0.001**	-0.093/0.161
Physical activity level	**0.698/0.001**	**0.624/0.001**	0.079/0.436
LOS	-0.004/0.965	-0.053/0.604	-0.108/0.286
Oxygen requirement	**-0.510/0.001**	**-0.439/0.001**	-0.090/0.373
Pneumonia	**-0.693/0.001**	**-0.607/0.001**	-0.102/0.313

Table 5: Correlation analysis between demographic and disease characteristics and, aerobic capacity measurements.
r: correlation coefficient.

It has already been shown that the lack of physical activity reduces the aerobic capacities of individuals due to quarantine practices and flexible work measures to prevent the spread of the pandemic[22-24]. In our opinion, the aerobic capacity and aerobic capacity change increase in correlation with the increase in the work activity level before the illness is the most important result of our study. We think that this result shows that continuing physical activity, even at home, will increase recovery after the illness, so home exercise programs should be encouraged at the social level.

Besides, characteristics including the duration of hospital stay, the number of drugs used, the presence of pneumonia, and the need for oxygen were associated with the aerobic capacity measured at the beginning of the treatment and in the 3rd month. These parameters are interrelated parameters that show a more severe course of the disease. In the presence of severe lung involvement, the number of drugs used increases, the duration of hospital stay is prolonged, and some patients need oxygen[25]. However, the critical point here is that aerobic capacity change is not affected even with severe lung involvement. Studies have reported that lung lesions in COVID-19 pneumonia patients can be entirely absorbed during short-term follow-up[26].

Our study has several limitations. As we aimed to evaluate the patients and the disease characteristics that may affect aerobic capacity, each parameter was evaluated separately. However, our results need to be proven for each parameter because we cannot evaluate each parameter's relationship with other parameters (for example, the smokers may have a young age, have no comorbidity, and high work activity level). Nevertheless, the present study may provide clues for better diagnostic, therapeutic, and preventive approaches to COVID-19.

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