

Effects of Short-Term Physiotherapy in Hospitalized COVID-19 Patients Infected with Mutant and Non-Mutant Virus: A Prospective Study

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ABSTRACT

Aim: The aim of study, to assess the short term effects of physiotherapy on patients infected with mutant and non-mutant SARS-CoV-2 virus.

Material and Methods: The patients included in the study were analyzed in two different groups. Patients infected with non-mutant SARS-CoV-2 were in Group 1 (n=16; age=53.81±9.48). Patients infected with mutant SARS-CoV-2 were included in Group 2 (n=16; age=55.25±10.12). Physiotherapy which included mobilization, normal range of motion, and a breathing exercise program, was performed on both groups (Group 1: Median=7.00; Min-Max=5-20 days; Group 2: Median: 7.00; Min-Max=4-15 days). All patients underwent a once-daily physiotherapy program. The patients' muscle strength, mobility, activities of daily living, exercise capacity, and perception of fatigue were evaluated. The mixed repeated measures ANOVA model was used to compare groups.

Results: It was found that physiotherapy improved muscle strength, mobility, ability to perform activities of daily living, exercise capacity, and perception of fatigue in both groups (p<0.05). Additionally, results for the evaluations including muscle strength (p=0.791), ADL (p=0.410), and mobility (p=0.124) were similarly favorable in both groups. There was no significant change in heart rate and SpO2 after the intervention in both group (p>0.05).

Conclusion: The current study showed that a short term physiotherapy program was as successful in patients infected with mutant SARS-CoV-2 as it was in patients infected with non-mutant SARS-CoV-2. Physiotherapy is beneficial for COVID-19 disease, as it decreases functional limitation and symptoms of COVID-19 disease by contributing positively to muscle strength, mobility, activities of daily living, exercise capacity, and the perception of fatigue.

Keywords: Physical therapy modalities; COVID-19; fatigue; early ambulation.

Hastanede Yatan Mutant ve Mutant Olmayan Virus ile Enfekte COVID-19 Hastalarında Kısa Süreli Fizyoterapinin Etkileri: Prospektif Bir Çalışma

Öz

Amaç: Çalışmanın amacı, mutant ve mutant olmayan SARS-CoV-2 virüsü ile enfekte hastalar üzerinde fizyoterapinin kısa süreli etkilerini değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya dahil edilen hastalar 2 farklı grupta analiz edildi. Mutasyona uğramamış SARS-CoV-2 ile enfekte hastalar Grup 1'deydi (n=16; yaş=53,81±9,48). Mutasyona uğramış SARS-CoV-2 ile enfekte hastalar ise Grup 2'de (n=16; yaş=55,25±10,12) yer aldı. Her iki gruba da mobilizasyon, normal hareket açıklığı ve solunum egzersiz programını içeren fizyoterapi uygulandı (Grup 1: Medyan=7,00; Min-Max=5-20 gün; Grup 2: Medyan: 7,00; Min-Max=4-15 gün). Tüm hastalara günde bir kez fizyoterapi programı uygulandı. Hastaların kas kuvveti, mobilitesi, günlük yaşam aktiviteleri, egzersiz kapasitesi ve yorgunluk algısı değerlendirildi. Grupları karşılaştırmak için karma desenli tekrarlanan ölçümler ANOVA modeli kullanıldı.

Bulgular: Fizyoterapinin her iki grupta da kas kuvveti, mobilite, günlük yaşam aktivitelerini gerçekleştirme yeteneği, egzersiz kapasitesi ve yorgunluk algısını iyileştirdiği bulundu (p<0,05). Ek olarak, kas kuvveti (p=0,791), günlük yaşam aktiviteleri (p=0,410) ve mobilite (p=0,124) gibi değerlendirmelerin sonuçları da her iki grupta da benzer şekilde olumluydu. Her iki grupta da tedaviden sonra kalp hızı ve SpO2'de anlamlı bir değişiklik olmamıştır.

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Sonuç: Mevcut çalışma, kısa süreli fizyoterapi programının mutasyona uğramış SARS-CoV-2 ile enfekte hastalarda, mutasyona uğramamış SARS-CoV-2 ile enfekte hastalarda olduğu kadar başarılı olduğunu göstermiştir. Fizyoterapi, kas kuvveti, mobilite, günlük yaşam aktiviteleri, egzersiz kapasitesi ve yorgunluk algısına olumlu katkı sağlayarak COVID-19 hastalığının fonksiyonel kısıtlılığını ve semptomlarını azalttığı için COVID-19 hastalığında faydalıdır.

Anahtar Kelimeler: Fizik tedavi modaliteleri; COVID-19; yorgunluk; erken ambulasyon.

INTRODUCTION

SARS-CoV-2, which leads to COVID-19, can cause cough, nausea, fever, vomiting, shortness of breath, myalgia, fatigue, arthralgia, headache, diarrhea, and very rarely arthritis (1, 2). Individuals inpatient with mild to severe COVID-19 may suffer for a long time deficits such as poor breathing capacity, weakening of pulmonary and extremity muscles, decreased ability to perform routine activities, and limited ability to walk (3). Due to the wide range of potential symptoms, treating these functional deficits beginning in the acute phase necessitates multi-professional rehabilitation interventions (4). According to recent studies, the recovery of individuals who need healthcare in hospitals depends greatly on the physiotherapy team (5).

Rehabilitation, when implemented early, can significantly reduce the duration of ventilatory support and hospitalization, enabling patients to resume their daily activities sooner. Physical ambulation and therapy in the ICU have been shown to improve muscle strength, mobility, and reduce hospital stay by up to one hundred eighty days (6).

A mutation is a change in a genome's DNA or RNA sequences that offers a novel phenotypic and/or genotypic advantage, increasing a virus or pathogen's virulence and/or survival rate. Coronaviruses are classified into four genera based on their phylogeny: Alpha-CoV, Beta-CoV, Gamma-CoV, and Delta-CoV (7).

While the virus was initially more aggressive in older persons, after it mutated, it affected every ages and all sections of society, leading to an increase in the amount individuals who need intensive care therapy (8). Mutations allow this virus to improve its spread, change its infection potential, and escape the host's immune system, hence modifying the immunologic reaction and causing resistance against therapies (9). SARS-CoV-2 variations have more spread than the initially identified strain, making it harder to control the virus and the sickness in Turkey as well as in other countries (10, 11). So the process for treatment and prevention may need to be reevaluated. The current study is to compare the effects of short-term physiotherapy in hospitalized COVID-19 patients infected with mutant and non-mutant SARS-CoV-2 virus.

MATERIAL AND METHODS

The prospective study was carried out at Ankara City Hospital, Internal Medicine inpatient clinic. The study comprised 32 patients aged 18 to 65 who were hospitalized, patients infected with mutant (Alpha, Beta, and Gamma viruses) (n = 16) and non-mutant (n = 16) SARS-CoV-2 virus, and who wanted to participate in a

physiotherapy program during hospitalization. Analyses of functional outcome criteria were conducted on patients with stays of at least 72 hours. Participants who had an exercise contraindication, experienced several organs failing, had an acute illness, were uncooperative, or were on PEG were excluded.

N/F swab samples taken from the patients were sent to the Ankara City Hospital Molecular Microbiology Laboratory in a viral nucleic acid transport (vNAT) rapid extraction tube. In addition to SARS-CoV2, the study also investigated mutant forms of the viruses Alpha, Beta, and Gamma. Therefore, the patients included in the study were divided into two categories.

Patients infected with non-mutant SARS-CoV-2 were in Group 1, while patients infected with mutant SARS-CoV-2 were in Group 2. Following the first evaluation, a physiotherapy program was applied to both groups during their hospitalization. Initial assessments were repeated at discharge.

All procedures were followed by the Helsinki Declaration's ethical guidelines and principles. Ankara City Hospital's Ethical Committee provided approval dated 31.03.2021 and numbered E1-21-1644. Patients in the study provided informed consent. Clinical trial number of the study is NCT05874076.

The patients were interviewed, and their medical record was reviewed to collect demographic and clinical characteristics. Global muscle strength, activities of daily living, and mobility were assessed for each patient. Exercise capacity and treatment-related hemodynamic responses were also assessed. Detailed descriptions of clinical and functional evaluations are provided below. To reduce variability, all outcome measures were evaluated by only one physiotherapist.

Muscle strength was evaluated using the Medical Research Council (MRC) scale. The muscles in the lower and upper extremities are evaluated bilaterally using this scale. A total of 6 major muscle groups are evaluated, and each muscle group is scored from 0 (no contraction) to 5 (normal contraction). Below 48 scores indicates muscle weakness; the highest score is 60, also minimal clinically important difference is 4 points (12).

Activities of daily living were assessed with the Katz Index of Independence in Activities of Daily Living (KATZ ADL). The independence levels of patients in basic daily activities like bathing, using the restroom, dressing, feeding, and transfer are examined using this scale. The scoring on the scale ranges from 0 (dependent) to 6 (independent) (13).

The Rivermead Mobility Index (RMI) was utilized for mobility assessment. The RMI is a 15-item, one-dimensional index with a progression from turning over in bed to running ability. A total point ranges from 0 to 15 for the index. 14 points or less indicate mobility problems (14).

Exercise capacity was evaluated with the 5-repetition sit to stand test (5STS). Even though the 5STS measures functional mobility and lower extremity performance, studies have revealed a correlation between the 5STS and the 6-minute walk test (15, 16). The test calculates the amount of time (in seconds) needed to stand up five times from a seated position on the chair as quickly as feasible.

All study patients received COVID-19 pharmaceutical treatment according to admission recommendations while hospitalized. Following a consultation with physiotherapy, patients underwent a once-daily mobilization, normal range of motion, and breathing exercise program until discharge. A patient-based (consistent clinical profile and steady respiratory and hemodynamic performance) five-stage protocol was utilized during mobilization, starting with sitting in bed and ending with walking (17). Joint range of motion exercises were conducted either passively, actively-assisted, actively, or with resistance, with the goal of either maintaining or improving joint integrity, range of motion, and muscle strength. A patient's tolerance (fatigue) and hemodynamic response (heart rate, peripheral oxygen saturation) was guided all interventions and progress. Fatigue perception was evaluated with the modified Borg Scale. There are 12 values on this scale, from 0 to 10. The perceived difficulty level increases as the score rises (18).

Statistical Analysis

The analysis of the data was carried out with the IBM SPSS v.22 (IBM Corp., Armonk, NY, USA) program. Categorical variables were presented as n (%), normally distributed variables as mean \pm standard deviation, and non-normally distributed variables as median [min-max].

The Shapiro-Wilk test was used to examine the normality of the data distribution. Based on the distribution of each variable, Student's t-test or Mann-Whitney U test was used in comparisons of Group 1 and Group 2. Paired Sample t-test or the Wilcoxon test was used for in-group comparisons. A mixed model repeated measures analysis of variance was performed to determine the main effect and interactions of normally distributed variables between groups. The sphericity and homogeneity assumptions were also sought for this analysis in addition to the normality assumption. Categorical variables were compared between groups using Chi-square test or Fisher's exact test. In all analyses, the $p < 0.05$ level of statistical significance was considered.

RESULTS

A study calculated the effect size of the muscle strength improvement based on the MRC score to be 0.71 (19). With this value, a minimum of 15 participants in each effect size of 0.71. Thirty-two patients, 16 from Group 1 and 16 from Group 2, took part in the study (Figure 1).

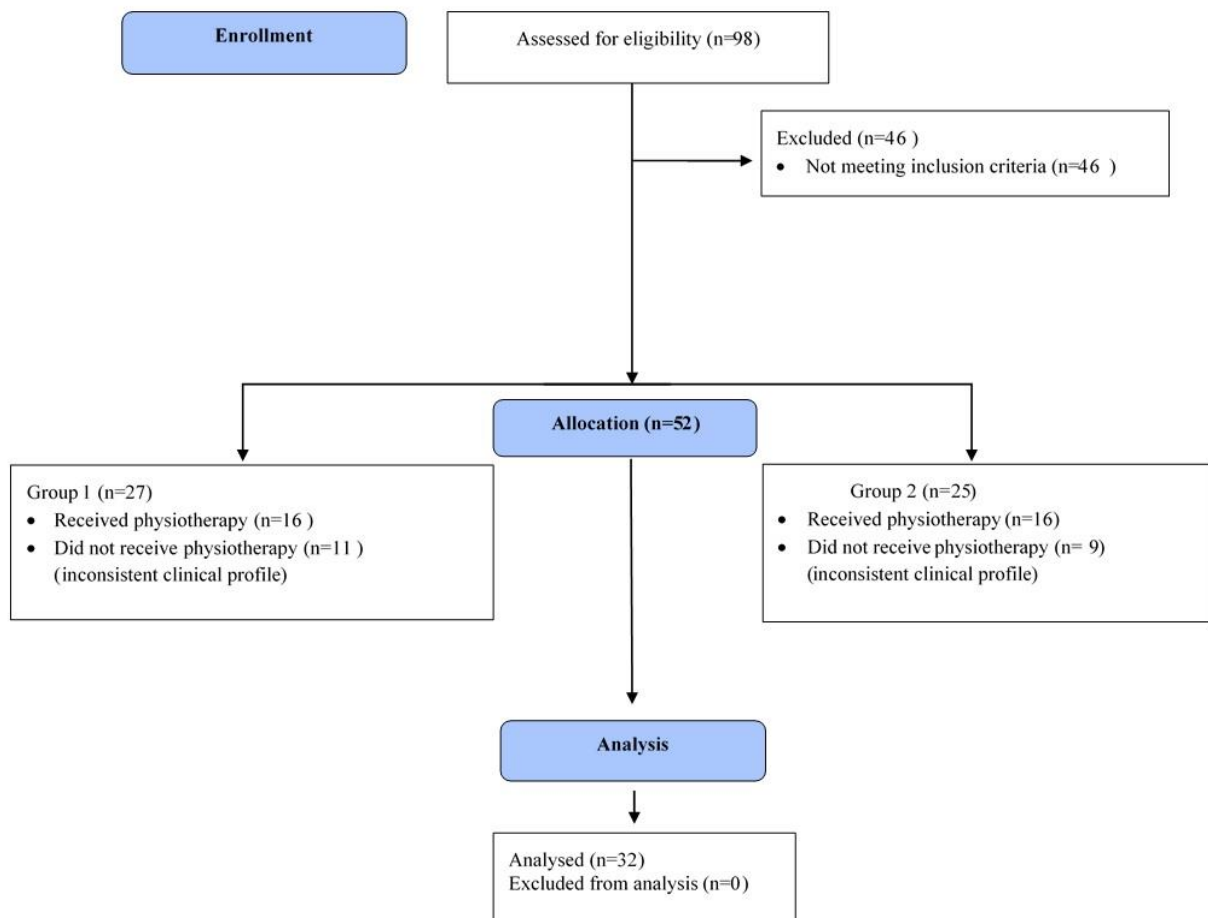


Figure 1. Flow chart of study participants

Most of the patients are male (n=26 (81.25%), with an mean age of 53.81±9.48 and 55.25±10.12 in Group 1 and Group 2, respectively. The clinical characteristics of the

patients were similar between the groups (p>0.05), as presented in Table 1.

Table 1. Clinical characteristics of patients

	Group 1 (n=16)			Group 2 (n=16)			p value
	Mean±SD/ [min;max]	n (%)	Median	Mean±SD/ [min;max]	n (%)	Median	
Age (years)	53.81±9.48			55.25±10.12			0.682 ^a
Sex							
Female	1 (6.20)			5 (31.20)			0.172 ^b
Male	15 (93.80)			11(68.80)			
BMI	28.01±4.06			30.01±3.15			0.131 ^a
Duration of education	12.06±4.95			11.50±4.58			0.741
Comorbidity score	0.00 [0;3]			0.00 [0;4]			0.235 ^a
Length of stay in hospital (days)	0.00 [0;0]			1.00 [1;1]			0.897 ^a
Length of stay in ICU(days)	0.00 [0;30]			0.00 [0;7]			0.867 ^c
Duration of physiotherapy (days)	7.00 [5;20]			7.00 [4;15]			0.491 ^a
Respiratory supports							
No	2(12.50)			1(6.30)			0.431 ^d
Nasal cannula	9(56.30)			13(81.30)			
Oxygen mask	4(25.00)			2(12.50)			
Non-rebreathing mask	1(6.30)			0(0)			
Laboratory tests							
CRP (mg/L)	11.40±22.66			8.65±12.71			0.423 ^a
LDH (U/L)	330.31±98.67			293.63±86.37			0.272 ^a
D-DİMER	0.72±0.84			0.70±0.86			0.724 ^a
Procalcitonin (ng/mL)	0.42±1.42			0.04±0.02			0.402 ^a
Fibrinogen (mg/dL)	4.09±1.02			3.59±0.97			0.170 ^a

^a: Student's t-test. ^b: Chi-square test ^c: Mann Whitney U test. ^d: Fisher's exact test. BMI: Body Mass Index. CRP:C-Reactive Protein. ICU: Intensive Care Unit. LDH: Lactate Dehydrogenase.

After intervention, MRC muscular strength scores significantly improved in both groups (p<0.05). Improving were similar between groups, and there was no significant group ×time effect for the variable (p=0.791). The mixed repeated measures ANOVA model showed no significant group× time interaction for the KATZ ADL scale (p=0.410), but ADL were significantly improved in both groups post-intervention compared to pre-intervention (p<0.001). The mixed repeated measure ANOVA model

revealed no significant interaction effects of group x time for mobility (p=0.124). Within-group analyses showed that both groups had significantly increased Rivermead mobility scores post-intervention compared to pre-intervention (p<0.001). There were no significant differences in mobility scores between groups. Muscle strength, ADL, and mobility outcome data are presented in Table 2.

Table 2. Comparison of muscle strength, activity of daily living and mobility pre and post intervention

	Group 1 (n=16) Mean±SD	Group 2 (n=16) Mean±SD	Group ×Time p^a	Group p^a	Time p^a	ηp2
MRC-muscle strength						
Pre-intervention	53.75±9.54	53.50±8.14				
Post-intervention	56.31±5.32	56.43±4.89	0.791	0.980	<0.001	0.339
<i>p^b</i>	0.034	0.004				
In-group Change (Δ)	2.56±4.38	2.93±3.51				
KATZ						
Pre-intervention	2.00±2.09	2.19±1.94				
Post-intervention	4.75±1.43	5.44±0.89	0.410	0.393	<0.001	0.770
<i>p^b</i>	<0.001	<0.001				
In-group Change (Δ)	2.75±1.77	3.25±1.61				
RIVERMEAD						
Pre-intervention	5.75±3.43	5.81±3.25				
Post-intervention	10.38±3.81	12.00±2.09	0.124	0.416	<0.001	0.800
<i>p^b</i>	<0.001	<0.001				
In-group Change (Δ)	4.62±2.80	6.18±2.78				

MRC: Medical Research Council. ^a: Mixed model repeated measures analysis of variance. ^b: Paired Sample T-test

Before the intervention, 75% of the patients in Group 1 and 68.7% of the patients in Group 2 could not complete the 5STS (Figure 2). The rates were 12.5% and 6.25% after the intervention, respectively. Changes in heart rate, SpO₂, and perception of fatigue during testing were similar both within and between groups ($p>0.05$). In the pre- and post-intervention periods, the resting heart rate, SpO₂, and Borg

fatigue perception levels of the patients in both groups were similar ($p>0.05$). There was no significant change in heart rate and SpO₂ after the intervention; however, the perception of fatigue decreased significantly in both groups ($p<0.05$). Hemodynamic and fatigue perception response data to intervention and exercise testing are shown in Table 3.

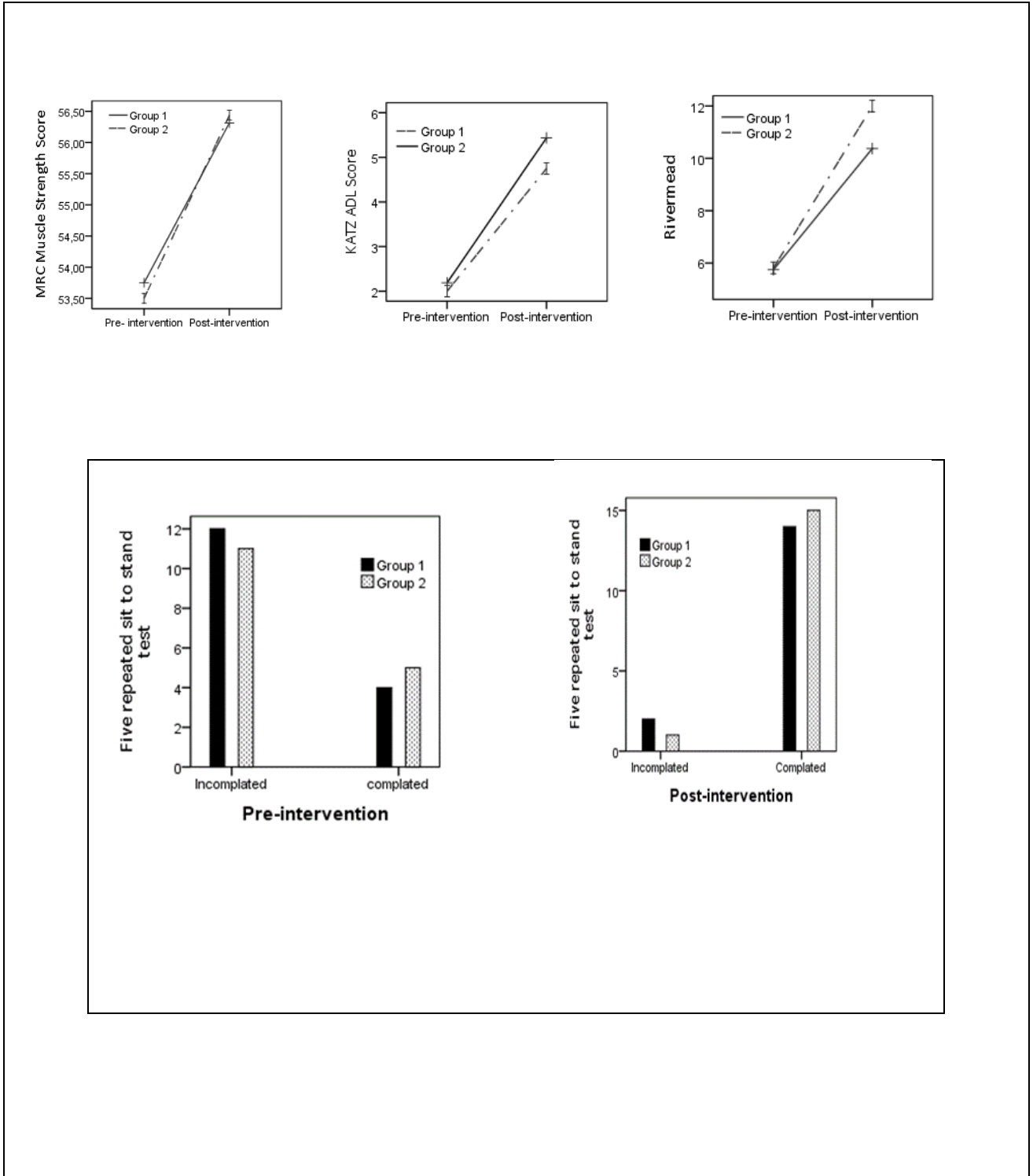


Figure 2. Change responses to treatment outcome measures between group

Table 3. Hemodynamic and fatigue perception responses to intervention and exercise testing

		Group 1 (n=16)			Group 2 (n=16)					
		Pre-intervention Median [Min;Max]	Post-intervention Median [Min;Max]	<i>p</i> ^b	In-group Change (Δ) Median [Min;Max]	Pre-intervention Median [Min;Max]	Post-intervention Median [Min;Max]	<i>p</i> ^b	In-group Change (Δ) Median [Min;Max]	Between groups difference <i>p</i> ^a
5STS		0.00 [0;21]	14.69 [0;19]	0.021	13.68 [-20;19]	0.00 [0;30]	12.43 [0;20]	0.065	10.00 [-16;16]	0.073
Resting Heart rate	Heart rate	90.00 [66;110]	83.50 [70;115]	0.102	-4.50 [-17;30]	93.00 [65;122]	90.00 [64;122]	0.284	-2.00 [-23;24]	0.539
Heart rate change during test	Heart rate change during test	11.00 [-8;49]	6.00 [1;48]	0.756	3.50 [-36;17]	10.5 [-3;35]	5.00 [-13;34]	0.211	-2.00 [-32;15]	0.224
Resting SpO ₂	SpO ₂	91.50 [90;98]	94.00 [89;99]	0.051	2.00 [-5;6]	92.50 [90;96]	94.00 [85;96]	0.261	0.50 [-5;4]	0.073
SpO ₂ change during test	SpO ₂ change during test	-5.00 [-12;-1]	-3.00 [-19;0]	0.083	1.00 [-9;7]	-6.50 [-15;3]	-3.50 [-15;0]	0.175	1.00 [-7;9]	0.809
Resting Borg Fatigue	Borg Fatigue	2.00 [0;9]	0.50 [0;5]	0.020	-1.00 [-9;2]	2.00 [0;8]	2.00 [0;5]	0.042	-0.50 [-4;2]	0.539
Borg Fatigue change during test	Borg Fatigue change during test	1.00 [0;6.5]	1.00 [0;4]	0.718	0.00 [-5;3]	2.50 [1;7]	2.00 [0;5]	0.324	-1.00 [-5;2]	0.590

a: Mann Whitney U Test. b: The Wilcoxon test. 5STS: Five repeated sit to stand test. SpO₂: peripheral oxygen saturation

DISCUSSION

This prospective study is the first investigation comparing the effects of physiotherapy in patients infected with mutant and non-mutant SARS-CoV-2 virus. It was found that physiotherapy improved muscle strength, mobility, ability to perform ADL, exercise capacity, and perception of fatigue in both groups in a hospital setting. In light of this, the current study points to the significance of early physiotherapy in COVID-19 patients.

Although different guidelines and recommendations have been made around the world to reduce the physical deficits of COVID-19 with earlier physical therapy, a small number of investigations have been conducted to investigate the impacts of physiotherapy in inpatient COVID-19 individuals. Our results supported early reports from around the world. A study conducted in 2020 in Romania on hospitalized patients diagnosed with COVID-19, It was found that combining active physiotherapy with pharmaceutical treatment considerably reduced symptoms such as dry cough and dyspnea (3).

In the current study, patients infected with mutant and non-mutant SARS-CoV-2 virus were included in the early physiotherapy program. Physiotherapy was performed for a median of 7 days in Group 1 and 7 days in Group 2. Although it was observed that the motor performances of the patients in both groups were impaired at the time of admission, significant improvement was found in motor performance tests at the time of discharge from physiotherapy.

Bed rest can result in fast muscular atrophy and deconditioning (20). After two weeks of immobility, young healthy adults experience a 5–9% decline in quadriceps muscle mass and a 20–27% decrease in quadriceps muscle strength, according to studies (21, 22). We did not expect as few patients to have an MRC score of less than 48 when admitted (about 25%). A cross-sectional investigation with 60 COVID-19 survivors who required inpatient rehabilitation after ICU care indicated that 72.70% of them had muscle weakness, a prevalence that was significantly greater than ours (23). The short ICU length of stay may partially explain this situation in our study. Although the baseline MRC score was not very low,

we found that physiotherapy yielded benefits in muscle strength in both groups.

The Rivermead Mobility Index showed that the patients' mobility in both groups had improved significantly from the start of physiotherapy. Our findings were consistent with an earlier study conducted by Rossi et al. (24) in people with COVID-19 admitted to the ICU. When patients were examined using the Mobility Score at the end of physiotherapy performed for a median of 8 days, 10.7% showed no change, 40.2% improved by 2 points, and 49.0% improved by more than 3 points compared to baseline in the study.

KATZ was noticeably low at the time of admission into physiotherapy, with the patients even losing all autonomy for activities of daily living in this study. The patients' everyday tasks improved significantly, as did their muscle strength as well as mobility upon discharge. These findings were consistent with a retrospective study of the first 100 patients admitted to the COVID-19 rehabilitation department (25). In this study, the mean length of the rehabilitation stay was 9.85 days. It was found that there was an improvement in the grip strength and activities of daily living of the patients with the rehabilitation program. It was known that 5STS was substantially linked with measures of exercise capacity, lower limb strength, health-related quality of life, and dyspnea in patients with stable COPD (21). The baseline physical condition and exercise capacity of our patients were low, as 75% of the patients in Group 1 and 68.7% of those in Group 2 could not complete the 5STS. At discharge, this percentage reduced to 12.5% and 6.25%, representing a considerable improvement in physical condition and exercise capacity. Also, there was no significant change in heart rate or SpO₂ following the physiotherapy, but both groups' perception of fatigue decreased. In another study, in which 42 patients received inpatient rehabilitation for 32.00;26.00 days, there was a significant improvement in muscle strength, fatigue, exercise capacity, and the ability to perform activities of daily living in line with our study (26).

Up to 70% of COVID-19 patients with a history of moderate to severe disease have reported experiencing

fatigue, which interferes with daily activities and quality of life (26-28). Therefore, improvement of the perception of fatigue is important for COVID-19 patients. In a study examining the role of patient-specific rehabilitation (30 minutes/set, 2 times/day) in hospitalized COVID-19 patients, significant improvement was found in activities of daily living and perception of fatigue, which is consistent with our study (29).

These findings are highly noteworthy and reflect the potential advantages for these individuals of an early physiotherapy program. Patients are advised to begin mobilizing actively at the earliest safe opportunity during their battle with COVID-19. Despite this proactive approach, full recovery may not be attained upon discharge, signaling the potential need for ongoing outpatient physiotherapy. Additionally, no adverse effects were reported during the physiotherapy sessions, further highlighting its safety. The use of mobilization was found possible and safe as an intervention to enhance muscle function and strength in ICU patients, and there have been very few side events also reported in the literature (17, 30). This research has several limitations. Firstly, due to the lack of a control group, it is not possible to determine the cause of the reported results. Conducting a clinical trial comparing physiotherapy to a "sham physiotherapy" control group was not seen as ethical. Secondly, this research had a small sample. Patients whose functional evaluations could not be completed due to rapid patient turnover were not included in the analysis. However, there was enough data to demonstrate pre-post and between-group statistical differences. Lastly, the results of the current study are presented from a single hospital. However, since this study was conducted in Ankara, one of the largest cosmopolitan cities in Turkey, it also includes a patient population with a very different clinical course.

CONCLUSION

The COVID-19 epidemic is the most significant health emergency in recent decades. In particular, mutations can make treatment more difficult, so treatment strategies may be necessitated. If physiotherapy is performed by a physiotherapist according to take into account the patient's current status (e.g., stable clinical presentation with stable respiratory and hemodynamic function), it is beneficial and safe for patients infected with mutant and non-mutant SARS-CoV-2 virus to regain their functional independence. After a thorough examination and a personalized inpatient physiotherapy program, we identified highly significant improvements in muscle strength, exercise capacity, and functional deficits in our study. After discharge, outpatient rehabilitation may also be recommended for patients with minor deficits and minimal functional impact. There have been few studies on the rehabilitation of COVID-19 patients to date, and more research is needed in this field to provide more effective rehabilitation for such patients.

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