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The Effect of Early Rehabilitation on COVID-19: A Prospective, Observational Study

Erken Rehabilitasyonun COVID-19 Üzerine Etkisi: Prospektif, Gözlemsel Çalışma

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Abstract

Objective: The aim of this study was to investigate the effect of early pulmonary rehabilitation (PR) on the course of the disease, respiratory functions, physical activity, fatigue, and discharge time in Coronavirus disease-2019 (COVID-19) patients in the intensive care unit (ICU) setting.

Method: A total of 31 patients (20 females, 11 males) with COVID-19 confirmed by real-time polymerase chain reaction who were admitted to the ICU were included. Demographic, clinical, and laboratory data of the patients were recorded. Physical activity, dyspnea, and fatigue of all patients were evaluated before and after PR program. All patients were evaluated on the day of PR in the ICU, the day of discharge from ICU to the ward, and on the day of discharge from hospital. Functional status was evaluated using the functional disability questionnaire (FDQ), the ambulation status using the functional ambulation classification (FAC), dyspnea using the modified Borg scale (MBS), and fatigue using the fatigue severity scale.

Results: The mean length of ICU and hospital stay was 17.93±11.54 days and 18.29±8.41 days, respectively. The mean number of sessions was 8.87±7.66. The mean time from hospitalization to recovery was 13.00±9.62 days. Median FDQ and MBS scores were significantly higher during the ICU stay than the ward stay and at the time of discharge (p<0.05). Median FAC scores were significantly higher at the time of discharge than the ward and ICU scores (p<0.05). There was a positive and statistically significant correlation between the FDQ scores during the ward stay and C-reactive protein (CRP) values during the ICU stay (r=0.382, p=0.034) and CRP values during the ward stay (r=0.379, p=0.035). There was a

Öz

Amaç: Bu çalışmanın amacı, yoğun bakım ünitesinde (YBÜ) yatan Koronavirüs hastalığı-2019 (COVID-19) hastalarında erken pulmoner rehabilitasyonun (PR) hastalığın seyri, solunum fonksiyonları, fiziksel aktivite, yorgunluk ve taburculuk süresi üzerindeki etkisini araştırmaktır.

Yöntem: Çalışmaya gerçek zamanlı polimeraz zincir reaksiyonu ile doğrulanmış COVID-19 tanılı olup YBÜ'ye yatışı yapılan toplam 31 hasta (20 kadın, 11 erkek) alındı. Hastaların demografik, klinik ve laboratuvar verileri kaydedildi. Tüm hastalarda PR programından önce ve sonra fiziksel aktivite, dispne ve yorgunluk değerlendirildi. Hastalar YBÜ'de PR'nin ilk günü, YBÜ'den servise taburcu edildikleri gün ve hastaneden taburcu edildikleri gün değerlendirildi. Fonksiyonel durum, fonksiyonel yetersizlik ölçeği (FYÖ), ambulasyon durumu fonksiyonel ambulasyon sınıflandırması (FAS), dispne modifiye Borg ölçeği (MBÖ) ve yorgunluk yorgunluk şiddet ölçeği ile değerlendirildi.

Bulgular: YBÜ ve hastanede kalış süresi sırasıyla 17,93±11,54 gün ve 18,29±8,41 gün idi. Ortalama seans sayısı 8,87±7,66 idi. Hastane yatışından iyileşmeye kadar geçen ortalama süre 13,00±9,62 gün idi. Medyan FYÖ ve MBÖ skoru, servis yatışına ve taburculuk esnasına kıyasla YBÜ yatışı sırasında anlamlı düzeyde daha yüksekti (p<0,05). Medyan FAS skoru, servis ve YBÜ skorlarına kıyasla, taburculuk sırasında anlamlı düzeyde daha yüksekti (p<0,05). Servis yatışı sırasında FYÖ skorları ve servis yatışı (r=0,379, p=0,035) ve YBÜ yatışı sırasında (r=0,382, p=0,034) C-reaktif protein (CRP) değerleri arasında pozitif ve istatistiksel olarak anlamlı bir ilişki izlendi. Taburculuk sırasında FYÖ skorları ve YBÜ yatışı sırasında ferritin düzeyleri arasında negatif ve istatistiksel olarak anlamlı bir ilişki

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Abstract

negative and statistically significant correlation between the FDQ scores at the time of discharge and ferritin levels during the ICU stay (r=-0.421, p=0.018). A positive and statistically significant correlation was observed between MBS scores at the time of discharge and CRP values during the ward stay (p=0.418, p=0.019).

Conclusion: Our study suggests that PR is an effective and safe approach with improved physical and functional results and COVID-19 survivors should undergo a PR program in an individualized manner using a multidisciplinary approach to improve short- and long-term outcomes.

Keywords: COVID-19, early rehabilitation, pulmonary rehabilitation, intensive care unit

Öz

görüldü (r=-0,421, p=0,018). Taburculuk sırasında MBÖ skorları ve servis yatışı sırasında CRP düzeyleri arasında pozitif ve istatistiksel olarak anlamlı bir ilişki tespit edildi (p=0.418, p=0,019).

Sonuç: Çalışmamız PR'nin fiziksel ve fonksiyonel sonuçlarda iyileşme sağlayan etkili ve güvenli bir yaklaşım olduğunu göstermektedir. COVID-19 geçiren hastalar, kısa ve uzun dönem sonuçlarda iyileşme elde etmek için multidisipliner bir yaklaşım ile bireysel olarak PR programına alınmalıdır.

Anahtar kelimeler: COVID-19, erken rehabilitasyon, pulmoner rehabilitasyon, yoğun bakım ünitesi

Introduction

On December 31st, 2019, pneumonia cases of unknown etiology in the city of Wuhan, Hubei province, China were reported by the China Office of the World Health Organization. On January 7th, 2020, the causative agent was defined as a new coronavirus which was not identified in human before and it was named novel Coronavirus disease-2019 (COVID-19), due to its close resemblance to severe acute respiratory disease-coronavirus-2 (SARS-CoV-2) (1,2). The first COVID-19 case in Turkey was reported in March 11th, 2020 (3). The virus dramatically affected all over the world and the number of infected individuals increased rapidly. By the end of August 2022, a total of 1,629,517 confirmed cases were reported with 99,678 deaths.

The SARS-CoV-2 infection may be asymptomatic or it may cause a wide spectrum of symptoms, such as mild symptoms of upper respiratory tract infection and life-threatening sepsis (4). It can damage multiple systems such as cardiovascular, gastrointestinal, nervous and musculoskeletal systems (5). According to the Turkish national guidelines, pneumonia and severe pneumonia are the criteria for admission to the intensive care unit (ICU) (6).

The main goal of pulmonary rehabilitation (PR) is to reduce disability in patients with lung disease and improve their quality of life, thereby reducing the burden on the healthcare system (7,8). In COVID-19, PR principles have been defined for acute, subacute, and post-COVID-19 rehabilitation (9). Early rehabilitation has been shown to have a positive effect on the recovery of patients with COVID-19 (10,11).

In the present study, we aimed to investigate the effect of early PR on the course of the disease, respiratory functions, physical activity, fatigue, and discharge time in COVID-19 patients in the ICU setting.

Materials and Methods

Study Design and Study Population

This single-center, prospective, observational study was conducted at the Department of Physical Medicine and Rehabilitation (PMR) of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, between March 2021 and April 2022. A written informed consent was obtained from all participants. The study was approved by the institutional Ethics Committee and the Republic of Turkey, Ministry of Health and conducted in accordance with the principles of the Declaration of Helsinki.

Patients infected with COVID-19 as confirmed by real-time polymerase chain reaction who were admitted to the ICU were included. All patients who were eligible for PR program were evaluated by a PMR specialist. Inclusion criteria were as follows: A fraction of inspired oxygen (FiO_2) of <60% (0.6); oxygen saturation (SpO_2) of >90%; respiratory rate of ≤40 breaths/min; positive end-expiration pressure of ≤10 cmH_2O; systolic blood pressure of ≥90 to ≤180 mmHg; mean arterial pressure of ≥65 to ≤110 mmHg; and heart rate of ≥40 to ≤120 bpm. All patients were extubated before inclusion in the PR program. Exclusion criteria were as follows: Fever (≥38.5 °C); >50% disease progression within 24 to 48 hours on radiological imaging of the lungs; severe cardiac problems such as heart failure, arrhythmia, bundle branch block, and cardiac involvement; renal or hepatic failure with progressive deterioration of the renal or hepatic functions; congenital musculoskeletal deformities which prevent mobilization; malignancies; rheumatic diseases; psychological disorders; resting blood pressure of <90/60

or >140/90 mmHg; receiving mechanical ventilation (MV) support; having shock evidence (lactic acid ≥4 mmol/L); new-onset unstable deep vein thrombosis and pulmonary embolism; a suspicion of aortic stenosis. Finally, a total of 44 patients who met the inclusion criteria were included.

Data Collection

Demographic data such as age and sex, clinical data, and laboratory data of the patients such as hemoglobin, hematocrit, white blood cell count, platelet count, C-reactive protein (CRP), lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase (AST), D-dimer, fibrinogen, procalcitonin, ferritin, cortisol, urea, creatinine, partial pressure of oxygen (pO_2), and SpO_2 were recorded. Physical activity, dyspnea, and fatigue of all patients were evaluated before and after PR program. The PR was applied to the patients during the entire hospital stay by experienced physiotherapists. All patients were evaluated on the day of PR in the ICU, on the day of discharge from ICU to the ward, and on the day of discharge from hospital.

PR Protocol

The PR protocol was applied for a week with varying durations based on the performance of each individual patient. The protocol consisted of breathing exercises (10 reps every 2 hours daily), postural drainage, percussion, and vibration (three times daily), secretion excretion and coughing (three times daily), respiratory muscle training (Triflo) (10 reps every 2 hours), positioning, in-bed mobilization (5 reps three times daily), bedside mobilization (5 reps three times daily), and postural exercises (5 reps three times daily). All patients were given a home-based PR program after discharge including postural exercises, lifestyle modifications, and walking exercises.

Assessment

Physical activity, dyspnea, and fatigue of all patients were evaluated before and after the PR program. Functional status was evaluated using the functional disability questionnaire (FDQ). The ambulation status was assessed using the functional ambulation classification (FAC) (12), dyspnea was assessed using the modified Borg scale (MBS) (13), and fatigue was assessed using the fatigue severity scale (FSS) (14).

Statistical Analysis

Statistical analysis was performed using the SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation, median and interquartile range or number and frequency, where applicable. The normality of distribution of variables was checked using the Kolmogorov-Smirnov test. The Wilcoxon test was used to analyze non-parametric variables. The Spearman correlation analysis was performed to identify the correlation between the variables. A p-value of <0.05 was considered statistically significant.

Results

A total of 31 patients were included in the study. Of these patients, 20 were females and 11 were males. Six patients received high-flow nasal oxygen therapy, 13 received non-invasive ventilation, and 12 patients underwent endotracheal intubation. The mean length of ICU and hospital stay was 17.93±11.54 days and 18.29±8.41 days, respectively. The mean number of sessions was 8.87±7.66. The mean time from hospitalization to recovery was 13.00±9.62 days. Twenty-eight patients were able to breath room air during discharge, while two patients were discharged with non-invasive nasal mask and one with non-invasive mask with ventilation support (Table 1).

Biochemistry test results and FDQ, FAC, MBS, and FSS scores during ICU and ward stay and at the time of discharge are shown in Table 2.

As shown in Table 3, there was a statistically significant difference in the FDQ scores between the measurements during the ward and ICU stay ($p<0.001$), during the ward stay and at the time of discharge ($p<0.001$), and during the ICU stay and at the time of discharge ($p<0.001$). The median FDQ scores were significantly higher during the ICU stay than during the ward stay and at the time of discharge and significantly higher during the ward stay than the measurements at the time of discharge. In addition, there was a statistically significant difference in the median MBS scores between the measurements during the ward and ICU stay ($p<0.001$), between the ICU stay and at the time of discharge ($p<0.001$), and during the ward stay and at the time of discharge ($p<0.001$). The median MBS scores were significantly higher during the ICU stay than the ward and discharge scores and significantly higher during the ward stay than the scores at the time of discharge. Also, there was a statistically significant difference in the median FAC scores between the measurements during the ward and ICU stay ($p<0.001$), between the ICU stay and at the time of discharge ($p<0.001$), and between the ward stay and at the time of discharge ($p<0.001$). The median FAC scores were significantly higher at the time of discharge than the ward and ICU scores and significantly higher during the ward stay than the ICU scores.

Table 1. Demographic and clinical characteristics of patients

Variable		n	%
Sex	Male	20	64.5
	Female	11	35.5
Age	≤50 years	9	29.0
	51-60 years	10	32.3
	≥61 years	12	38.7
Alcohol use	Yes	4	12.9
	No	27	87.1
Smoking	Yes	5	16.1
	No	26	83.9
BMI	Underweight	1	3.2
	Normal	8	25.8
	Overweight	19	61.3
	Obesity	3	9.7
Intubation status	HFNO	6	19.4
	Niv mask	13	41.9
	Trx	12	38.7
Respiratory support ICU (n=34)	HFNO	27	79.4
	Niv mask	3	8.8
	Niv nasal	4	11.8
Respiratory support ward (n=35)	Niv mask	16	45.7
	Niv nasal	15	42.9
	Room air	4	11.4
Respiratory support discharge	Niv mask	1	3.2
	Niv nasal	2	6.5
	Room air	28	90.3
Comorbidities (n=44)	None	13	29.5
	CVD	6	13.6
	CKD	2	4.5
	Diabetes	7	15.9
	Hypertension	11	25.0
	Asthma	2	4.5
	Thyroid disease	3	6.8
Mean ± SD			
Age, year			58.80±13.68
BMI, kg/m²			26.04±3.73
LOS in ICU, day			17.93±11.54
PR session in ICU, n			8.87±7.66
LOS in ward, day			18.29±8.41
Time to mobilization, day			13.00±9.62
PR session in ward, n			12.25±6.55
Total PR session, n			21.12±10.42

BMI: Body mass index, HFNO: High-flow nasal oxygen, Niv: Non-invasive, trx: Tracheostomy, CVD: Cardiovascular disease, CKD: Chronic kidney disease, LOS: Length of stay, ICU: Intensive care unit, PR: Pulmonary rehabilitation, SD: Standard deviation

Table 2. Biochemistry test results and FDQ, FAC, MBS, and FSS scores during ICU and ward stay and at the time of discharge

	ICU Mean ± SD	Ward Mean ± SD	Discharge Mean ± SD
FDQ	**57.87±5.60**	52.51±9.01	32.80±10.39
MBS	1.74±1.34	0.79±0.75	0.29±0.33
FAC	0.19±0.47	0.70±1.07	4.29±0.78
CRP, mg/dL	104.30±74.98	43.82±44.17	13.62±16.73
Lymphocyte count, x109/L	0.86±1.05	1.80±2.92	2.34±1.28
Neutrophil count, x109/L	12.89±4.52	10.50±12.74	5.97±2.62
Eosinophil count, x109/L	0.01±0.03	0.24±0.30	0.15±0.14
Ferritin, mL/ng	1240.10±1212.48	651.02±412.27	417.96±271.25
Procalcitonin, ng/mL	0.65±0.92	0.33±0.98	0.09±0.06
D-dimer, µg/mL	1.60±1.54	1.92±1.24	0.95±1.02

FDQ: Functional disability questionnaire, MBS: Modified Borg scale, FAC: Functional ambulation classification, FSS: Fatigue severity scale, ICU: Intensive care unit, SD: Standard deviation, CRP: C-reactive protein

Table 3. Comparison of FDQ, MBS, FAC scores during the ICU and ward stay and at the time of discharge

Variable	n	Median (IQR)	p-value*
FDQ-ICU	31	60.00 (8.00)	**<0.001**
FDQ-ward	31	55.00 (10.00)	
FDQ-ICU	31	60.00 (8.00)	**<0.001**
FDQ-discharge	31	30.00 (14.00)	
FDQ-discharge	31	30.00 (14.00)	**<0.001**
FDQ-ward	31	55.00 (14.00)	
MBS-ICU	31	2.00 (1.00)	**<0.001**
MBS-ward	31	0.50 (1.00)	
MBS-ICU	31	2.00 (1.00)	**<0.001**
MBS-discharge	31	0.00 (0.50)	
MBS-discharge	31	0.00 (0.50)	**<0.001**
MBS-ward	31	0.50 (1.00)	
FAC-ICU	31	0.00 (0.00)	**0.001**
FAC-ward	31	0.00 (1.00)	
FAC-ICU	31	0.00 (0.00)	**<0.001**
FAC-discharge	31	4.00 (1.00)	
FAC-discharge	31	4.00 (1.00)	**<0.001**
FAC-ward	31	0.00 (1.00)	

*Wilcoxon test. p<0.05 indicates statistical significance.
IQR: Interquartile range, FDQ: Functional disability questionnaire, MBS: Modified Borg scale, FAC: Functional ambulation classification, ICU: Intensive care unit

The correlation analysis results of FDQ, MBS, FAC, CRP, and ferritin are shown in Table 4. Accordingly, there was a positive and statistically significant correlation between the FDQ scores during the ward stay and CRP values during the ICU stay (r=0.382, p=0.034) and CRP values during the ward stay (r=0.379, p=0.035). In addition, there was a positive and statistically significant correlation between the FDQ scores at the time of discharge and CRP during the ward stay (r=0.383, p=0.034) and a negative and statistically significant correlation between the FDQ scores at the time of discharge and ferritin levels during the ICU stay (r=-0.421, p=0.018). Furthermore, a positive and statistically significant correlation was observed between the MBS scores at the time of discharge and CRP values during the ward stay (p=0.418, p=0.019).

The correlation analysis results of FDQ, MBS, FAC, lymphocyte, neutrophil, and eosinophil counts are given in Table 5. Accordingly, there was a positive and statistically significant correlation between the FDQ scores at the time of discharge and eosinophil count during the ward stay (r=0.399, p=0.026). In addition, a negative and statistically significant correlation was observed between the FAC during the ward stay and eosinophil count during the ward stay (r=-0.423, p=0.018).

There was a negative and statistically significant correlation between the FDQ scores during the ward stay and procalcitonin levels at the time of discharge (r=-0.411, p=0.22). In addition, there was a negative and statistically significant correlation between FAC during the ICU stay and D-dimer values during the ward stay (r=-0.368, p=0.041) and at the time of discharge (r=-0.469, p=0.008) (Table 6).

Discussion

In the present study, we investigated the effect of early PR on the course of the disease, respiratory functions, physical activity, fatigue, and discharge time in COVID-19 patients in the ICU setting. Our study results showed that early PR could improve physiological and functional results of COVID-19 patients.

Previous studies have shown that many patients infected with COVID-19 suffer from limited physical functions, as well as respiratory and psychological dysfunctions (15). Nearly 5% of COVID-19 patients are severe cases requiring ICU care and 71% are critically ill patients with acute respiratory distress syndrome or sepsis requiring MV support (16,17). Pulmonary injuries are major complications of COVID-19 (18). In particular, prolonged MV is associated with secondary lung damage (19,20). Nearly half of patients suffer from obstructive pulmonary patterns and develop restrictive pulmonary disease following hospitalization (21,22). All these effects have been shown to be linked to decreased functional capacity and impaired quality of life.

Early rehabilitation refers to rehabilitation interventions that are initiated immediately after stabilization (23). It has been shown that early rehabilitation and mobilization can improve respiratory muscle strength, decrease functional impairments, and yield more satisfactory outcomes (24,25). In the current study, we applied the early PR protocol for a week with varying durations based on the performance of each individual patient. The protocol consisted of breathing exercises, postural drainage, percussion, and

Table 4. Correlation analysis results of FDQ, MBS, FAC scores, CRP, and ferritin levels

		FDQ/ ICU	FDQ/ ward	FDQ/discharge	MBS/ ICU	MBS/ ward	MBS/ discharge	FAC/ ICU	FAC/ward	FAC/discharge
CRP-ICU	r	0.151	0.382*	0.128	0.053	-0.037	0.286	-0.218	0.017	-0.086
	p	0.417	**0.034**	0.492	0.777	0.844	0.119	0.239	0.926	0.646
CRP-ward	r	0.061	0.379*	0.383*	0.104	0.147	0.418*	-0.435*	-0.169	-0.325
	p	0.746	**0.035**	**0.034**	0.578	**0.429**	**0.019**	**0.014**	0.364	0.074
CRP-discharge	r	0.018	0.084	0.332	-0.161	-0.121	0.071	-0.351	-0.137	-0.332
	p	0.922	0.652	0.068	0.385	0.515	0.704	0.053	0.463	0.068
Ferritin-ICU	r	0.188	0.068	-0.421*	0.001	0.170	-0.064	-0.117	-0.200	0.335
	p	0.312	0.717	**0.018**	0.996	0.360	0.731	0.532	0.282	0.065
Ferritin-ward	r	-0.055	-0.124	-0.246	-0.194	-0.114	-0.079	0.185	0.101	0.339
	p	0.771	0.507	0.182	0.297	0.542	0.674	0.320	0.589	0.062
Ferritin-discharge	r	-0.024	-0.249	-0.321	-0.029	-0.040	-0.038	0.317	0.184	0.220
	p	0.899	0.178	0.079	0.875	0.832	0.840	0.082	0.323	0.234

*Significant at p<0.05 (Spearman correlation analysis), FDQ: Functional disability questionnaire, MBS: Modified Borg scale, FAC: Functional ambulation classification, ICU: Intensive care unit, CRP: C-reactive protein

Table 5. Correlation analysis results of FDQ, MBS, FAC scores, lymphocyte, neutrophil, and eosinophil counts

		FDQ/ ICU	FDQ/ ward	FDQ/ discharge	MBS/ ICU	MBS/ ward	MBS/ discharge	FAC/ ICU	FAC/ ward	FAC/ discharge
Lymphocyte-ICU	r	0.012	0.108	0.040	0.324	0.107	0.076	-0.047	-0.095	0.065
	p	0.948	0.562	0.830	0.075	0.568	0.684	0.800	0.610	0.729
Lymphocyte-ward	r	0.084	0.345	0.268	0.259	0.291	0.142	0.014	-0.011	0.116
	p	0.654	0.057	0.146	0.160	0.112	0.445	0.940	0.953	0.533
Lymphocyte-discharge	r	0.233	0.190	-0.041	0.489**	0.305	0.219	0.106	-0.112	0.069
	p	0.207	0.305	0.826	**0.005**	0.095	0.237	0.571	0.547	0.711
Neutrophil-ICU	r	-0.137	-0.125	0.121	-0.105	-0.269	-0.183	0.218	0.250	0.084
	p	0.461	0.504	0.515	0.574	0.143	0.326	0.239	0.175	0.652
Neutrophil-ward	r	-0.112	0.185	-0.252	-0.071	-0.001	-0.063	-0.065	-0.162	0.300
	p	0.549	0.319	0.172	0.706	0.995	0.735	0.726	0.384	0.101
Neutrophil-discharge	r	-0.254	-0.020	0.165	-0.002	0.038	0.019	-0.016	0.170	-0.036
	p	0.168	0.914	0.374	0.993	0.839	0.921	0.933	0.362	0.846
Eosinophil-ICU	r	0.059	0.105	0.032	0.403*	0.403*	0.147	0.071	-0.262	-0.180
	p	0.751	0.573	0.865	**0.024**	**0.025**	0.431	0.704	0.155	0.332
Eosinophil-ward	r	0.309	0.132	0.399*	0.325	0.379*	0.379*	-0.381*	-0.423*	-0.371*
	p	0.091	0.480	**0.026**	0.074	**0.036**	**0.035**	**0.034**	**0.018**	**0.040**
Eosinophil-discharge	r	0.076	-0.272	-0.078	-0.037	-0.155	-0.168	-0.156	-0.043	-0.027
	p	0.686	0.138	0.676	0.842	0.406	0.367	0.401	0.820	0.884

*Significant at p<0.05 (Spearman correlation analysis), **Significant at p<0.01 (Spearman correlation analysis): FDQ: Functional disability questionnaire, MBS: Modified Borg scale, FAC: Functional ambulation classification, ICU: Intensive care unit

Table 6. Correlation analysis results of FDQ, MBS, FAC scores, procalcitonin and D-dimer levels

		FDQ/ ICU	FDQ/ ward	FDQ/discharge	MBS/ ICU	MBS/ward	MBS/ discharge	FAC/ ICU	FAC/ward	FAC/discharge
Procalcitonin-ICU	r	-0.120	-0.025	-0.058	-0.270	-0.111	-0.133	-0.129	-0.134	-0.013
	p	0.520	0.894	0.757	0.142	0.553	0.475	0.488	0.473	0.943
Procalcitonin-ward	r	0.181	0.209	0.182	-0.014	-0.039	0.060	-0.244	-0.198	-0.284
	p	0.329	0.259	0.328	0.940	0.835	0.748	0.186	0.285	0.122
Procalcitonin-discharge	r	-0.214	-0.411*	0.183	-0.057	-0.076	-0.128	0.141	0.089	-0.349
	p	0.247	0.022	0.325	0.762	0.686	0.491	0.450	0.635	0.054
D-dimer-ICU	r	0.176	0.083	0.124	0.167	0.229	0.057	-0.219	-0.237	-0.259
	p	0.344	0.657	0.505	0.369	0.216	0.759	0.236	0.200	0.159
D-dimer-ward	r	-0.107	-0.055	0.350	0.024	0.077	0.049	-0.368*	-0.105	-0.287
	p	0.566	0.771	0.054	0.896	0.682	0.794	**0.041**	0.575	0.117
D-dimer-discharge	r	0.196	0.117	0.248	0.092	0.087	-0.017	-0.469**	-0.358*	-0.319
	p	0.292	0.532	0.178	0.623	0.642	0.929	**0.008**	**0.048**	0.081

*Significant at p<0.05 (Spearman correlation analysis), **Significant at p<0.01 (Spearman correlation analysis): FDQ: Functional disability questionnaire, MBS: Modified Borg scale, FAC: Functional ambulation classification, ICU: Intensive care unit

vibration, secretion excretion and coughing, respiratory muscle training, positioning, in-bed mobilization, bedside mobilization, and postural exercises. Also, all patients were given a home-based PR program after discharge including postural exercises, lifestyle modifications, and walking exercises. We evaluated physical activity, dyspnea, and fatigue of all patients before and after the PR program. Our study results showed that the median FDQ scores were significantly higher during the ICU stay than the ward stay and at the time of discharge and significantly higher during the ward stay than the discharge scores. In addition, the median MBS scores were significantly higher during the ICU stay than the ward and discharge scores and significantly higher during the ward stay than the discharge scores. Also, the median FAC scores were significantly higher at the time of discharge than the ward and ICU scores and significantly higher during the ward stay than the ICU scores. These findings are consistent with previous study findings suggesting that early rehabilitation after COVID-19 is effective with significant improvements in functional outcomes (26,27).

Several studies have shown the benefit of early inpatient rehabilitation after ICU admission among COVID-19 survivors (28,29). In a retrospective study, physical and occupational therapy was found to be feasible in the ICU setting for COVID-19 patients (30). In another study, early mobilization effectively shortened the time to extubation and length of hospital stay with improved quality of life (31). Despite concerns about the rehabilitation of severe COVID-19 pneumonia cases, a consensus has been established recently including PR (32). As increased spontaneous breathing is associated with decreased intrathoracic pressure and pulmonary edema (33), the main goal of PR is to protect the lungs in severe COVID-19 cases (34).

In previous studies, D-dimer, CRP, and serum ferritin levels have been shown to be linked to COVID-19 severity and mortality (35,36). In a study, decreased diffusing capacity of the lungs for carbon monoxide (DLCO) was found to be most prevalent respiratory function impairment and ferritin level was found to be a significant clinical factor (37). Similarly, in our study, we found a negative and statistically significant correlation between the FDQ scores at the time of discharge and ferritin levels during the ICU stay. In addition, we observed a negative and statistically significant correlation between the FAC during the ICU stay and D-dimer values during the ward stay and at the time of discharge. We also found a positive and statistically significant correlation between the FDQ scores during the ward stay and CRP values during the ICU and ward stay.

Study Limitations

Nonetheless, there are some limitations to this study. First, it has a single-center study with a relatively small sample size and, therefore, the results should be cautiously interpreted. Second, there is no control group which precludes evaluating the rehabilitation effect on clinical outcomes. Third, long-term functional outcomes were unable to be assessed. Further multi-center, large-scale studies are needed to draw more reliable conclusions on this subject.

Conclusion

COVID-19 survivors should undergo PR in an individualized manner during the hospitalization to minimize the adverse outcomes of the disease. Based on our study findings, PR is an effective and safe approach with improved physical and functional results. Therefore, it seems to be a promising intervention for patients with COVID-19. However, we recommend a multidisciplinary approach to improve short- and long-term outcomes. Further large-scale prospective studies are warranted to elucidate which PR protocol is more effective in this group of patients.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital, between March 2021 and April 2022. The study was approved by the institutional Ethics Committee and the Republic of Turkey, Ministry of Health and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: A written informed consent was obtained from all participants.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: I.Ü., M.V., S.Ç., İ.D.A., G.O.H., Design: I.Ü., M.V., S.Ç., İ.D.A., G.O.H., Data Collection or Processing: İ.D.A., S.B., T.A., E.K., F.A., Analysis or Interpretation: F.A., İ.D.A, I.Ü., Drafting Manuscript: I.Ü., M.V., S.Ç., G.O.H., Critical Revision of Manuscript: İ.D.A, T.A., S.B., E.K., F.A., Final Approval and Accountability: I.Ü., M.V., S.Ç., G.O.H., T.A., İ.D.A., E.K, S.B., F.A., Technical or Material Support: T.A., S.B., İ.D.A., E.K., S.B., F.A., Supervision: I.Ü., M.V., S.Ç., G.O.H., Writing: I.Ü., M.V., S.Ç., G.O.H., T.A., İ.D.A., E.K, S.B., F.A.

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