



ORIGINAL ARTICLE

The role of acute rehabilitation in COVID-19 patients

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ABSTRACT

BACKGROUND: In the published literature there is scarce data on the importance of acute rehabilitation in patients suffering from COVID-19 disease.

AIM: Evaluation of the feasibility of respiratory and neuromuscular rehabilitation treatment in stable acute COVID-19 inpatients.

DESIGN: The study was designed as an observational prospective investigation of two cohorts respectively identified as Mild/Moderate and Stable Severe COVID-19 disease. All patients received a rehabilitation treatment consisting of breathing exercises, range of motion exercises and strengthening exercises, with the main difference in intensity and progression of treatment, depending on individual capacity of patient.

SETTING: Inpatients with diagnosed mild to moderate, or stable severe COVID-19 infection were included in the study.

POPULATION: Acute COVID-19 inpatients.

METHODS: Patients were divided into two groups depending on the severity of disease: "mild to moderate group" (MMG) and "stable severe group" (SSG). Functional outcomes included the Barthel Index (BI), Six Minute Walk Test (6MWT), Borg Scale for dyspnea, "Time Up and Go" Test (TUG), "Sit To Stand" test (STS), "One Leg Stance Test" (OLST) and Beck Depression Inventory (BDI) were evaluated at baseline and after rehabilitative treatment, on discharge.

RESULTS: We included 147 acute COVID-19 inpatients (75 male and 72 female), mean aged 63.90±13.76 years. There were noticeable statistically significant improvements in all observed measurements in both groups. Comparison between groups showed significant difference in MMG compared to SSG in all functional outcomes: TUG (P<0.001), STS (P<0.001), OLST (P<0.001), BDI (P=0.008), BI (P<0.001), and Borg scale for dyspnea (P<0.001). Despite the significant improvements of BI in SSG, the obtained values showed that the patients were still not functionally independent.

CONCLUSIONS: Acute respiratory and neuromuscular rehabilitation program is a feasible, but also effective and safe method for improving functional status in patients with COVID-19 infection.

CLINICAL REHABILITATION IMPACT: Results of the present study implicate that a supervised early rehabilitation program, implemented in the treatment of patients with COVID-19 disease in the acute phasis a feasible way for significant improvement of patient's functional outcomes. Early rehabilitation should be included into clinical protocols for the treatment of patients with COVID-19.

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KEY WORDS: Rehabilitation; COVID-19; Inpatients.

Coronavirus disease (COVID-19), caused by SARS-CoV-2 virus, is still spreading all over the world, with insufficiently known consequences, devastating human life and health.

The first case of COVID-19 infection in Serbia was re-

ported in March 2020. Since then, over 2.3 millions of cases have been confirmed, with a mortality ratio of 0.72%. Although the epidemiological situation is stable at the moment, every day physicians deal with the treatment of new cases or of the persisting consequences of the disease,

even months after the initial infection. This proportion makes COVID-19 uncontrollable disease despite apparent improvements in some rehabilitation strategies, diagnostic and treatment procedures and some research initiatives. Although the COVID-19 is most often followed by an acute respiratory syndrome, it could also have different clinical manifestations, including cough, fever, myalgia, arthralgia, digestive, neurological, cardiac or psychological disorders and other manifestations.¹

The disease can be categorized into five groups based on the severity of the infection: asymptomatic, mild, moderate, severe and critical COVID-19 infection. However, we shouldn't forget that the patient's clinical status may change over time.² Most patients still don't require hospitalization, because they develop mild symptoms or are asymptomatic. On the other hand, some patients with comorbidities such as obesity, hypertension, diabetes, chronic respiratory disease, malignancy, develop severe forms of illness, requiring mechanical ventilation and specific treatment in intensive care units (ICU).³ These patients are at greater risk of developing consequences of prolonged bed rest: muscle atrophy, deconditioning, fatigue, joint stiffness, immobilization syndrome and pain leading to reduced quality of life. Specialists in Physical Medicine and Rehabilitation have a key role in the multidisciplinary treatment of these patients. It is well known that acute respiratory and neuromuscular rehabilitation is necessary to improve body functions (such as muscle strength, endurance, or cognitive and emotional functions), and reduce the limitations in activities and participation. Due to social isolation or long hospital stay, associated with non-use or bed rest, some patients, especially elderly, may experience anxiety, depression or even cognitive decline.⁴ As reported in the literature, rehabilitation in the acute and post-acute phase would be helpful to diminish the sequelae of COVID-19 infection. Several authors suggest that early mobilization improves respiratory function helping maintain oxygen saturation levels.^{5, 6}

Some researchers proposed rehabilitation protocols for inpatients, consisting of early mobilization, strengthening and endurance training⁷⁻⁹ and balance exercises,⁹ with the aim of reducing weakness and dependency. However, one of the major obstacles to implementing acute rehabilitation treatment of patients with COVID-19, is a reluctance of the rehabilitation team, due to the contagious nature of the disease. Although, currently, COVID-19 preventive interventions are implemented on different levels, the increased caution against infection still exists.

Unfortunately, there is a lack of well-designed acute rehabilitation programs for COVID-19 patients and there is no published data to determine the efficacy of breathing exercise, range of motion and strengthening exercise in COVID-19 patients.

This aim of this study was to evaluate the effects of an early rehabilitation program in patients with mild to severe but stable COVID-19 disease on functional outcomes.

Materials and methods

We performed an observational prospective investigation of two cohorts, respectively identified as Mild/Moderate and Stable Severe COVID-19 disease. All patients, hospitalized in a non-ICU had been assessed for several functional outcomes, before and after an acute rehabilitation program. The study protocol was approved by the Ethics Committee of the Institute for Rehabilitation, in Belgrade (Serbia), protocol number 02/269-1, reviewed and approved by ClinicalTrials.gov identifier (NCT05619666). All participants were informed about the study design, and only after getting their written informed consent we physically examined and included them in the study. During the study period, we took care of protecting their privacy and anonymity of the respondent's data, in compliance with national and international guidelines.

Inclusion criteria were: 1) positive pharyngeal or nasal swab test for SARS CoV-2, obtained by PCR method; 2) patients older than 18 years; 3) SpO₂>94% on admission; 4) body temperature under 37.5 °C; 5) clinical stability defined by the ability to perform bedside active mobilization without a reduction of oxygen saturation (SpO₂) below 92%; 6) ability to move independently, without any assistance.

Exclusion criteria were: 1) SPO₂<94% on admission; 2) moderate and severe heart failure (grade III and IV, NY heart Association); 3) paresis or plegia as a result of cerebrovascular insult (CVI) or neurodegenerative disease; 4) impaired cognitive status.

Based on the severity of COVID-19 disease,² patients were divided into 2 groups: Group 1 (mild to moderate group, MMG) and Group 2 (stable severe group, SSG).

Patients from both groups started the rehabilitation program first day after admission. All patients included in the study were hemodynamically stable and the treatment was determined as safe. Until discharge from the hospital, a re-evaluation of neuromuscular and respiratory function was performed.

We included patients affected by COVID-19 disease whose diagnosis was confirmed by PCR testing (nasopharyngeal swab).

ryngeal swab) prior to the hospitalization in the non-intensive care hospital. During the whole rehabilitation period, the patients were COVID-19 positive and tested weekly (PCR test, nasal swab) in order to confirm the acute phase of disease.

The number of days of hospitalization was measured and evaluated according to the severity of the clinical symptoms, and not only according to the PCR test. The length of the rehabilitation treatment depended on the clinical symptoms of the patient and not only on the PCR test results. Initially, these were patients moderate degree of COVID-19 disease, with the need for medical care in hospital conditions and continuous monitoring of vital parameters, thus after clinical examination and triage they were sent to our COVID hospital. The median length between symptom onset and hospitalization ranging between 3 and 11 days. All participants at the admission had medical history with clinical examination, that included X ray, electrocardiogram (ECG) and echocardiogram, gas analysis, laboratory analysis (D-dimer, C reactive protein, CRP), fibrinogen, lactate dehydrogenase (LDH), leucocyte count, blood chemistry: creatinine. Upon admission physiatrist collected detailed anamnestic and demographic data and performed functional tests. Anamnesis consisted of set of questions regarding to the risk factors such as comorbidities, weight, height, Body Mass Index (BMI), habits: smoking, alcohol etc. All participants received low molecular weight heparin (LMWH) cortisone therapy, while some of them also received oxygen therapy (nasal cannula or oxygen mask). If they needed continuous airway pressure/bilevel positive airway pressure (CRAP/BIPAP) ventilation, they were sent to another hospital, enriched with that kind of equipment. Antiviral and vitamin therapy patients had already received,¹⁰ before they came to our non-invasive hospital unit. All patients were examined by an Internist and Physiatrist. Physiatrist were in charge for clinical monitoring of patients and assessment of whether the patient met the basic criteria for inclusion in the appropriate rehabilitation program.

Rehabilitation treatment for both groups (MMG and SSG) consisted of breathing exercises, range of motion exercises to maintain general and segmental mobility of the upper and lower extremities and strengthening exercises, with the main difference in intensity and progression of treatment, depending on individual capacity of patient. Rehabilitation treatment for patients in MMG group started with diaphragmatic breathing exercise. Patients were advised to do breathing exercises an upright sitting or semi-sitting position with one hand placed at the

top of the abdominal area and the other, at the top of the upper thorax. During breathing patients had to keep the neck and shoulders relaxed. They had to be concentrated on outward abdominal movement during inspiration and inward abdominal movement during expiration. The emphasis was on the expansion of the lower part of the chest. The patients were told to do deep inspiration through the nose with a passive prolonged expiration with a contracted half-open mouth with an accent on longer duration of the expiratory phase. If patients had to expel sputum and reduced cough, they used forced expiratory techniques, with a sealed plastic bag to avoid virus transmission.

Patients did breathe exercises for 5 minutes, every day, 2 times per day for the whole in-patient period of time (an average about 15 days). After breathing exercises patient did exercises for peripheral circulation for 5 minutes and range of motion exercises. In this phase patients performed active exercises to maintain the range of motion for upper and lower extremities, lasting 5-10 minutes.

Afterward they did strength exercises, that included: calf raises 6-8 times, semisquats 6-8 times, wall push up 6-8 times in 1-2 series. The frequency of strength training was once per day, each of 30-35 minutes duration, with the intention of not induce fatigue of the trained muscle groups.

Patients were advised to exercise at least one hour after eating. Also, they were told to stop training in case they feel any discomfort in the chest, dyspnea (Borg over 3), headache, profuse sweating, palpitations. Progression of the training was considered together with the patient, depending on the individual capacity. If the training went without difficulties, every 3 days the number of repetitions increased by 2. The resident of Physical and Rehabilitation Medicine (PRM) supervised the training.

Rehabilitation treatment implemented in the SSG comparing with the one implemented in MMG contained differences in intensity and progression of treatment, described below.

Patients from the SSG group had a portable oxygen support through the mask or nasal cannula. As in the previous group, the frequency of training was the same, patients exercised 5 days a week once per day, while breathing exercises were done twice a day, every day. Their rehabilitation program began with diaphragmatic breathing exercises with the aim of evacuating sputum and improving systematic oxygenation as well as circulation exercises to prevent embolic events. Then the warm-up phase continued, *i.e.* active exercises to maintain the range of motion of all joints. Strength exercises were the next phase in a

program: calf raises 4-6 times, semisquats 4-6 times, wall push up 4-6 times in 1-2 series, under the supervision of a resident and frequent measurement of peripheral saturation and number of respirations per minute. In case of fatigue of the patient, the training was intermittent.

The duration of the training was between 40 and 45 minutes, even if they had a lower number of repetitions, because these patients needed more time to implement the whole training. In this group of patients the intensity of the treatment was the same for the whole inpatients period (around 15 days), without progression in the number of repetitions.

At the end of the treatment, before discharge from the hospital, patients underwent a functional assessment and physical evaluation, as well as at the admission. All patients, from both groups were recommended to continue exercising at home, every day or at least 5 times per week with purpose to achieve the best musculoskeletal and respiratory recovery.

Functional status assessment of the patients was conducted using the following tests and question:

- Barthel index (BI) measured the independence and functional ability in activity daily living (ADL). The original 10-item form of the BI consisted of 10 common ADL activities including: feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing. Items were rated in terms of whether individuals can perform activities independently, with some assistance, or were dependent (scored as 10, 5 or 0). Maximal score of 100 indicated full independency, while the score lowest of 20 indicated total dependency.¹¹

- One Leg Stance Test (OLST) was used to assess static postural and balance control. The patients had to stand unassisted on one leg, with eyes opened and arms on the hips, and was timed in second from the time the one leg is lifted to the time when it touches ground. Patients who couldn't stand on one leg for more than 5 seconds were considered to be at an increased risk for falling and very poor balance.¹²

- The Timed Up and Go Test (TUG) was used for estimating the functional mobility of the lower limbs, as well as dynamic balance.¹² The test required from the patient to sit in the chair with his/her back against the chair back. On the command "go", the patient had to stand up from chair, walk 3 meters at the comfortable and safe pace, turn, walk back to the chair and sit down. Usually less than 12 seconds is needed for this activity.^{12, 13}

- A Sit-to-Stand (STS) Test was used to assess the

strength of lower extremities and functional independence, since the movement is part of the various Activities of Daily Living. Researchers have described its use as a measure of lower limb strength, balance control, fall risk and exercise capacity. For the STS patients were instructed to stand up and sit back down five times after each other as quickly as possible with their arms folded across their chest. The time was recorded from the start to the time the patient was seated again for the fifth time. A time of >14 s or the inability of performing the test correctly was considered abnormal.^{12, 13}

- Six-Minute Walk Test (6MWT) was used to assess cardiovascular and respiratory function, but also to assess the global systemic and peripheral circulation, as well as the response to exercise. The patient was required to walk quickly on a flat, hard surface for 6 minutes, while the walked distance, heart rate and blood pressure were measured before and after performing this activity.¹⁴

- Borg Scale for assessing dyspnea was used in clinical practice to measure perceived exertion and guide exercise intensity. The patient subjectively referred to his level of effort during exercise, between number 0 to 10, while 0 was causing as no difficulty at all, progressing to number 10, where breathing difficulty was maximal.^{15, 16}

- The Beck Depression Inventory (BDI) was used for measuring depression. The questionnaire contained 21 items on a 4-point scale from 0 (symptom absent) to 3 (severe symptoms). The minimum score was 0 and maximum score was 63. Higher scores indicated greater symptom severity. The results had been analyzed in accordance with 4-point adjective scale: 0-11 – no depression; 12-26 – mild depression; 27-49 – moderate depression; 50-63 – severe depression.¹⁷⁻¹⁹

Statistical analysis

All statistical analyses were performed using the SPSS package program version 20.0 (IBM corporation). Continuous data were presented as mean±standard deviation and frequency data as counts and percentages. The Kolmogorov-Smirnov Test was used for testing normality of dataset. The difference in numerical variables between groups was compared with independent t-test or Mann-Whitney Test, as appropriate. Comparisons between baseline and at discharge values of numerical variables was performed by the t-Test for paired samples. The mean difference between groups at the discharge was assessed by linear regression analysis (mean difference is reported as β). Change in functional assessments values were analyzed adjusted for baseline values of the measured param-

eter (Model 1), and baseline values of parameter and age (Model 2). The Chi-squared test and Fisher’s test were used to analyze categorical variables. All P values<0.05 (two-tailed) were considered significant. The complete-case analysis was performed without missing values imputation.

Participants

In this observational prospective investigation of two cohorts 205 patients were recruited for participation (Figure 1), while 147 patients were finally included and underwent the rehabilitation program. Six patients died, 21 patients declined to participate due to personal reasons (due to lack of motivation), 31 were transported to another department due to development of complications and worsening of the general condition.

Results

General clinical and demographic characteristics of COVID-19 inpatients

This study recruited 205 patients, but the entire rehabilitation program was carried out by 147 patients (72 women and 75 men) with an average age of 63.90±13.76 years (min 38, max 91 years). Demographic characteristics, comorbidities, and vaccine status of patients are presented in Table I. The average age was significantly higher in

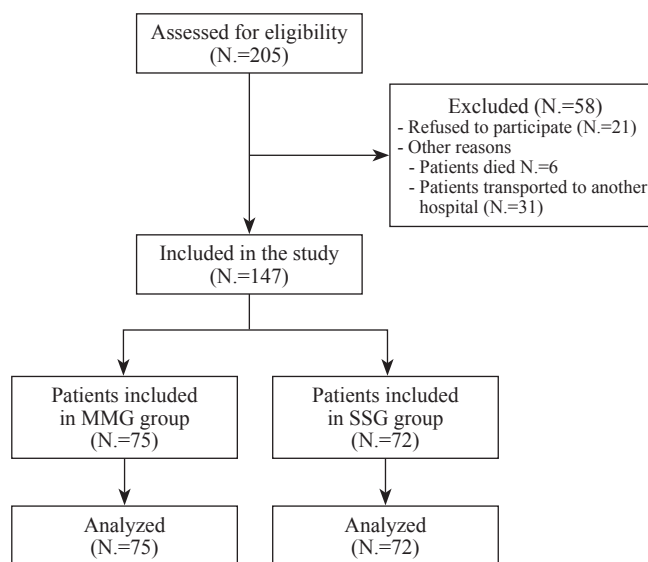


Figure 1.—Participants flowchart.

the SSG (70.58±12.76 vs. 57.48±11.62; P<0.001). At the time of hospitalization, the average days of illness were 7.68±2.63 in the MMG and 8.96±3.34 in the SSG (P=0.010). Patients from the MMG group were hospitalized more often for up to 10 days than the SSG group (72.0% vs. 33.3%, P=0.015). Other clinical characteristics presented in Table I did not differ statistically significantly between the groups (vaccination status, comorbidities).

TABLE I.—Demographic and clinical characteristics in MMG and SSG.

	Mild (MMG)		Severe (SSG)		P*
Age	57.48±11.62		70.58±12.76		<0.001
Gender					
Male	30	40%	42	58.3%	0.040**
Female	45	60%	30	41.7%	
Days of illness	7.68±2.59		8.96±3.29		0.010
Patients up to 10 days of hospitalization	54	72%	24	33.3%	<0.001
Patients between 10 to 20 days of hospitalization	18	24%	39	54.2%	<0.001
Patients with more than 20 days of hospitalization	3	4%	9	12.9%	0.114
Vaccination status	33	44%	24	33.3%	0.247
Sinopharm	21	28%	12	16.7%	0.147
Pfizer-Bionntech	3	4%	3	4.2%	1.000
Sputnik V	9	8%	9	12.5%	0.530
AstraZeneca	3	4%	0	0%	0.245***
Obesity	3	4%	3	4.2%	1.000**
Autoimmune disease	3	4%	0	0%	0.245***
Hypertension	33	44%	57	79.2%	<0.001**
Diabetes	24	32%	24	33.3%	1.000**
Chronic obstructive lung disease	0	0%	6	8.3%	0.012***
Arrhythmias	12	16%	15	20.8%	0.525***
Coronary disease	3	4%	12	16.7%	0.014***
Tumor	3	4.2%	0	0%	0.245***

*t-test, **Chi-squared test, ***Fisher’s Test.

TABLE II.—*Functional status and biochemical parameters of patients in MMG and SSG.*

	Time point	Mild	Severe	P*
C-reactive protein (mg/dL)	Admission	108.12±72.68	71.3±62.56	0.0012
	At discharge	3.49±4.62	10.48±22.60 ^a	<0.001**
Creatinine (µmol/L)	Admission	91.36±19.15	85.79±19.53	0.079
	At discharge	90.08±17.23	85.17±25.66	0.171
D-dimer (ng/mL)	Admission	1380.33±2130.48	1574.16±1228.18	0.005**
	At discharge	975.56±940.11	992.25±707.42 ^a	0.143**
Lactate Dehydrogenase (U/L)	Admission	289.36±99.5	296.67±131.7	0.889**
	At discharge	210.12±44.34 ^a	226.25±74.32 ^a	0.216**
Leucocytes (x10 ⁹ L)	Admission	7.78±4.09	7.56±3.23	0.613**
	At discharge	55.43±219.33	10.45±3.54 ^a	0.060**
Sedimentation (mm/hr)	Admission	68.88±33.62	60.04±30.91	0.116**
	At discharge	26.36±26.1 ^a	32.92±27.99 ^a	0.118**
Timed Up and Go Test (seconds)	Admission	15.06±3.47	23.03±4.54	<0.001
	At discharge	10.69±2.35 ^a	20.22±4.75 ^a	<0.001
Sit to Stand Test (seconds)	Admission	15.37±2.5	19.07±3.73	0.001
	At discharge	10.84±2.14 ^a	16.88±3.67 ^a	<0.001
One Leg Stance Test (seconds)	Admission	3.18±0.99	2.27±1.46	<0.001**
	At discharge	5.82±1.17 ^a	3.32±1.68 ^a	<0.001**
Back Depression Inventory (score range 0-63)	Admission	13.12±8.4	13±7.29	0.8612
	At discharge	8.56±7.62 ^a	14.46±7.64 ^b	<0.001**
Barthel Index (score range 0-100)	Admission	88.2±7.19	76.04±7.52	<0.001
	At discharge	97.20±3.25 ^a	82.92±8.45 ^a	<0.001
6 Minute Walk Test	Admission	464.68±41.71	292.50±53.67	<0.001
	At discharge	508.28±37.07 ^a	330.58±51.23 ^a	<0.001
Borg (score range 0-10)	Admission	2.52±0.65	3.62±0.65	<0.001**
	At discharge	0.52±0.51 ^a	1.58±0.58 ^a	<0.001**

*t-test, **Mann-Whitney Test; ^avs. discharge P<0.001, ^bvs. discharge P=0.012. Data are presented as mean±SD.

Changes during Rehabilitation treatment

At admission, the following values were statistically significantly different between the groups: CRP (P=0.001), D dimer (P=0.005), TUG (P<0.001), STS (P=0.001), OLST (P<0.001), BI (P<0.001), 6mwt (P<0.001) and BORG (P<0.001). The baseline values of the TUG, STS, OLST tests in the MMG group were 15.06±3.47; 15.37±2.5; 3.18±0.99, while in the SSG group they were 23.03±4.54; 19.07±3.73; 2.27±1.46, respectively.

At discharge, the following values were significantly different between the groups: CRP (P<0.001), TUG (P<0.001), STS (P<0.001), OLST (P<0.001), BDI (P<0.001), BI (P<0.001), 6mwt (P<0.001) and BORG (P<0.001) (Table II). At discharge, the values of the same tests in the MMG group were 10.69±2.35; 10.84±2.14; 5.82±1.17 and in the SSG 20.22±4.75; 16.88±3.67; 3.32±1.68; which showed the improvement within each group.

In the MMG, the following parameters were significantly changed during hospitalization: LDH, Se TUG, STS, OLST, BDI, BI, 6MWT and BORG (P<0.001 for all). In the SSG, during hospitalization, all examined parameters except creatinine, were significantly changed (P<0.001 for

all, except BEK: P=0.012) (Table II). The TUG, and STS significantly decreased after rehabilitation, followed by the increase of the OLST in both groups.

The baseline values of Bartel Index (BI) were 88.2±7.2 in the MMG and 76.04±7.52 in the SSG, while at discharge, these values were 97.2±3.25 and 82.92±8.45, respectively.

The baseline values of 6-MWT were 464.68±41.71m in the MMG and 292.50±53.67m in the SSG, while at discharge, these values were 508.28±37.97m and 330.58±51.23m, respectively.

Patients from the MMG at baseline scored Borg 2.52±0.65, while from the SSG 3.62±0.65. Rehabilitation led to decrease in Borg score to 0.52±0.51 in the MMG and to 1.58±0.58 in the SSG group.

At the baseline the average BDI in the MMG was 13.12±8.4, while in SSG was 13±7.29. At discharge, the BDI had significantly changed in both groups (in MMG: 8.56±7.62; in SSG 14.46±7.64).

Comparison between groups has shown that there was a statistically significant difference at discharge for the following parameters: the increase of TUG of 2.94 (P<0.001), the increase of STS of 2.97 (P<0.001), the decrease of OLST of

TABLE III.—The difference between MMG and SSG at discharge adjusted for baseline values of variables and age (linear regression analysis).

	At discharge – Model 1			At discharge – Model 2			At discharge – Model 3		
	Adjusted β	95%CI	P value	Adjusted β	95%CI	P value	Adjusted β	95%CI	P value
TUG (s)	2.94	2.17-3.70	<0.001	2.75	1.93-3.58	<0.001	2.67	1.82-3.52	<0.001
STS (s)	2.97	2.43-3.51	<0.001	3.03	2.42-3.64	<0.001	3.31	2.70-3.92	<0.001
OLST(s)	-1.74	-2.09-1.40	<0.001	-1.64	-2.03--1.26	<0.001	-1.68	-2.08--1.29	<0.001
BDI	5.99	4.55-7.43	<0.001	5.45	3.82-7.09	<0.001			<0.001
BI	-3.59	-5.78-.41	0.001	-3.75	-5.95--1.56	0.001	-4.27	-6.59--1.94	<0.001
6MWT	-22.45	-29.77-15.14	<0.001	-22.62	-30.00--15.24	<0.001	-23.96	-31.38--16.5	<0.001
Borg	0.67	0.43-0.91	<0.001	0.57	0.32-0.81	<0.001	0.51	0.30-0.71	<0.001

Adjusted β : unstandardized regression coefficient; Model 1: adjusted for baseline values of the tested parameter; Model 2: age and baseline values of the tested parameter; Model 3: age, baseline values of the tested parameter and length of stay.

1.74 ($P<0.001$), the increase of BEK of 5.99 ($P<0.001$), the reduction of BI of 3.59 ($P<0.001$), the decrease of 6mwt of 22.45 ($P<0.001$), and the increase of BORG of 0.67 ($P<0.001$) adjusted for baseline values of the tested parameter (Table III). The significant difference remained after adjustment for age in Model 2 and for the length of stay in Model 3.

Discussion

Results of the present study have shown that the rehabilitation program during acute phase of COVID-19 disease in mild to moderate as well as in stable severe inpatients, out of ICU units, is feasible and safe method for the patients as well as the medical staff and should be implemented in treatment protocols at non-intensive Covid units from the first day. After acute rehabilitation significant improvement of patient's functional outcomes is noted. Reduction in consequences of bed rest with improvement of neuromuscular and respiratory status, reduction of disability, improvement of psychological state and easier return of ADL has been revealed.

The feedback of therapists and patients also helped to identify success factors of the conducted acute rehabilitation program. Patients indicated that the supervised exercise program was beneficial to their recovery and motivation and encouraged them to extend this opportunity, emphasizing the importance of training, where the presence of physiotherapist contributed to the increase of patient's confidence and concentration.

The patients perceived the therapist's approach and the supervised program as supportive and as an acknowledgment for their problems. It helped them to recognize the balance between their capacities and demands of everyday life, which is perceived as a major problem that requires not only physical training but also attention to behavioral aspects. Thus, for those patient's whose potential for natu-

ral recovery is recognized, rehabilitation program should be available and implemented as a part of standard clinical care.

Personalized approach to the inpatients rehabilitation in accordance with their particular capabilities and taking into account their comorbidities is a way to avoid patient fatigue and unwanted events, as well as to achieve the best functional recovery. Thereafter, rehabilitation treatment that reduces disability, especially among the working population, affects economic trend.^{20, 21}

Knowing that the total hospital stay could be longer and the functional status on discharge worse in patients who did not have rehabilitation treatment encouraged us to share our results.

Recent study has shown that non-critical COVID-19 patients, complained about post-COVID symptoms.²² The results from the previous study had emphasized the importance of follow-up of patients with mild to moderate COVID-19 disease. It has been revealed that even patients with mild form of the disease required rehabilitation.

The multicenter prospective cohort study by Berentschot *et al.*, included patients who had been discharged from hospital, across four different rehabilitation settings: no rehabilitation, community-based rehabilitation, medical rehabilitation, and rehabilitation in a skilled nursing facility. Results of the study showed that patients with rehabilitation after hospital discharge improved in cardiorespiratory function, muscle strength, and mobility, whereas patients without rehabilitation improved only in muscle strength, which demonstrate the importance of rehabilitation.²³

Taking into account the before mentioned recommendations and consequences of COVID-19 and bed rest phenomena the rehabilitation program in our Center was designed. General recommendation for rehabilitation treatment were based on the clinical experience of a group of Physical Medicine and Rehabilitation specialists from

eleven different countries in Europe and North America⁷ as well as in accordance with the expert rehabilitation team from Italy, where they faced deleterious consequences of COVID-19 disease²⁴.

This study was performed in the non intensive COVID Unit and no control group was used, for the ethical reasons. Obviously, this limits the interpretation of the results, where the patient's natural potential for recovery must not be overlooked. Nevertheless, in accordance with our intentions, as well as ethical principles, this study provided a test of the feasibility and usability of acute rehabilitation treatment, with positive results. Moreover, it gave indications for starting acute rehabilitation, as well as successful features of the treatment and improvement of the patient's functional status after its application.

To the best of our knowledge, this is the first study showing the results of acute rehabilitation of a group of mild to moderate and stable severe COVID-19 inpatients in Serbia. Study results demonstrated that functional improvements after acute rehabilitation were significantly higher than before the rehabilitation program. This applied not only to the physical condition of patients and their subjective feeling wellbeing but also to the outcomes measured with TUG, STS, OLST, 6-MWT. Measuring ability to walk, sit or balance we objectively assessed the level at which the patient was functional in those activities as well as followed the recovery. Individually designed, multicomponent exercise program is feasible in acute COVID-19, non intensive units and needs to be proscribed in acute COVID-19 inpatients.

The most common symptoms of COVID-19 infection are of respiratory and neuromuscular system origin,²⁵ therefore rehabilitation program was carried out with the emphasis on respiratory training. By improving respiratory capacity and tissue oxygenation the maximum effect of physical training would be achieved. The study by Enright *et al.* showed that the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women.²⁶ In comparison with the present study results, although patients from this study improved their performance, (from 464.68±41.71 to 508.28±37.07 in first group; from 292.50±53.67 to 330.58±51.23 in second group) patients from the second, SSG did not achieve the average value for the healthy population. They have gone even further from a healthy person according to the results of the Study by Troosters *et al.*, which showed that the average value of 6 MWT was 630 m for 51 healthy people.²⁷ This comparison encouraged our rehabilitation team to advice patients to continue with learned exercise program at home every day, at least 5 times per week.

Li *et al.* reported an increase in 6-MWT after six weeks of rehabilitation of elderly patients (≥ 65 years) at least 6 months after the disease onset, with a mean increase of the walking distance of 50 meters),²⁸ which is very similar compared to our Study (50 meters vs. 44, 38 meters in our Study). On the other hand, Puchner *et al.* reported a significantly higher increase in 6 MWT in post-acute Covid 19-patients, with a mean increase of the walking distance of 176 meters.²⁹

The intensity of the training should be adapted to the patients ability in order to be safe and secure for them. This is the reason why a large number of studies recommend low intensity training for mild patients, which corresponds to the Borg Scale of dyspnea < 3 .^{30, 31} In our study patients were most often rated up to 3. However in the case when they were rated with 4 we didn't notice a drop in saturation below 92% with the oximeter, and we continued training albeit with pauses and more frequent measurement of SpO₂%. During this study a statistically significant increase in BI in both groups (in the first group from 88 to 97 and in the second group from 76 to 83) was noted. Tuba Guler *et al.* showed an even greater reduction in dependence than we did (from 44.8 to 88.4).³² On the other hand, a study by Curci *et al.*³³ showed that the increase in BI was not statistically significant after early rehabilitation in postacute inpatients. Although we noted significant improvement of BI in the SSG, the obtained values showed that the patients from this group were still not functionally independent.

By assessing the functional status of patients (TUG, STS, OLST) a statistically significant benefit in both groups is noted. In the studies of Bohannon *et al.* and Guralnik *et al.*, the value of the STS test < 14 s is considered abnormal.^{34, 35} In contrast to the MMG (15.37±2.5 and 10.84±2.14), the patients from the SSG, even after a significant improvement (19.07±3.73 and 16.88±3.67), failed to perform the STS Test for 14 s, which can be explained by reduced strength as a result of reduced physical activity.

It has been shown that depressive symptoms are common during the COVID-19 pandemic.³⁶⁻³⁸ In our study population, at admission, there was no significant difference between groups and mild symptoms of depression were noticed in both groups (13.12±8.4 in MMG and 13±7.29 in SSG). At discharge a significant improvement has been noted in MMG group, so we can conclude that for this group of patients' rehabilitation treatment had a beneficial effect on mental health as well.

By comparison of functional outcomes between MMG and SSG it is found that patients from the MMG had bet-

ter recovery that the patients from SSG. Patients from the SSG, beside beneficial effects that they reached, were still functionally independent and with mild depression, what suggest the need for longer rehabilitation treatment.

Patients in the groups were exposed to treatment for periods of different duration. However, the difference between MMG and SSG remained after adjustment of baseline functional status and treatment duration, implying that the functional outcome is likely not influenced by treatment duration and baseline values of functional tests. Our results are similar with those observed by Piquet *et al.*,³⁹ with the main difference in observing functional outcomes with different tests and a different duration of exercise. While in the previous study the authors observed Barthel index, 10 m sit-to-stands and grip strength, we revealed the functional outcomes with the following tests, 6MWT, BI, OLST, STS, TUG, Borg, BDI. Concerns about increases in mental health conditions, anxiety and depression worldwide, suggest the importance of this aspect of disease and the need of support. In that context, the present study included BDI Score for assessing patients mental health, while the same had not been observed in the previous study.

Bertolucci *et al.*⁴⁰ had been reported the features and rehabilitative outcomes of patients requiring rehabilitation due to disabilities related to severe COVID-19 infection, with mean length of stay 46 days, while in our study mild to moderate and severe stable COVID-19 patients were included, with different length of stay. Functional outcomes also scored with different functional tests, so the methodology had been different, but with the high recommendation for implementing rehabilitation in all COVID-19 patients.

Taking into account the results from mentioned above studies,^{39, 40} but also from our center, even with the little differences in methodology and functional outcomes, consistent recovery for patients (severe, mild and moderate) still positive for COVID-19, after rehabilitation treatment provided in sub-acute phase had been beneficial.

All the mentioned results of this study confirm the importance of identifying the most fragile patients on time and precisely defining functional outcomes of acute COVID-19 rehabilitation for this vulnerable group. Furthermore, post-acute rehabilitation had been advised to those patients. This is the first study showing the results of acute rehabilitation of a group of MMG and SSG patients, in such a large two cohorts of COVID-19 patients, where the effects of specially designed supervised rehabilitation program, have been proven by seven functional tests, presented above. The use of the mentioned rehabilitation

method may facilitate the development of effective acute rehabilitation strategies. In daily clinical practice, the shift from the “acute infection and isolation” to “multidisciplinary evaluation and therapeutic strategies” is critical to systematically defining the choice of COVID treatment towards the potentially most effective option for every patients in individual level.

The strength of the present study lays in the fact that it has a prospective design within patients divided in accordance with the WHO strategies, while the acute mobilization is recognized as very important goal. Patients approved with high compliance, despite the fact that COVID-19 disease complications might escalate rapidly.

Limitations of the study

There are certain limitations of this Study. The main limitation is the fact that this study represents a single center experience. In the period of time when we conducted the study, under pandemic circumstances, different centers had transformed organization on their own policy, therefore any implementation of new rehabilitation strategies was not feasible. Which made it impossible to conduct this study as a multicenter. The other limitation of the study is heterogeneity of the study group in terms of patient age, as well as different stage of disease and absence of control group. We considered that it would be unethical if one group of patients was deprived for rehabilitation treatment (in order to plan a control group). Also, our patients did not have neuropsychological support as fundamental activity, which could also be considered as limitation. Further limitation, owing to the method used in this study is absence of follow-up period for evaluating the effects of exercises on functional recovery, especially for the SSG. Although, all patients from the study were advised to keep conducting adopted rehabilitation program, post-acute COVID Centers could be connected with the Acute-COVID units with the same goal, to reach the maximum from exercise and to have adequate follow-up for these patients. Thereafter, Tele-rehabilitation should be adopted as an integral concept for the follow-up assessment in post COVID-19 patients.

Conclusions

This study, with its moderate size, carefully designed acute rehabilitation treatment demonstrated that a well-planned and monitored program of respiratory and neuromuscular rehabilitation is feasible and safe even in the acute phase of COVID-19 disease, in mild, moderate and stable severe

hospitalized patients. After acute rehabilitation treatment a significant improvement in patient's functional status is noted. Furthermore, the rehabilitation treatment needs to be implemented as a part of standard clinical care.

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