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Functional Capacity in COVID-19 Related Acute Respiratory Distress Syndrome Survivors

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Abstract

Objective: The aim of this retrospective study is to determine the functional capacity, global muscle weakness and quality of life in COVID-19 survivors.

Background: Acute respiratory distress syndrome survivors frequently develop impaired physical function, quality of life, and muscle weakness.

Method: Acute respiratory distress syndrome survivors related to COVID-19 underwent standardized physical clinical evaluation, Medical Research Council-sumscore, hand-grip strength, 6-minute walk test, 5 repetition-chair-stand test, timed up and go test and Short form-36 evaluation following 4-6 weeks after hospital discharge in Physical Medicine and Rehabilitation Outpatient Clinic.

Results: Fifteen patients (10 men, 5 women) with median age 69 years and length of intensive care unit stay 10 days were analyzed. There were impairments in 6-minute walk test, 5 repetition-chair-stand test, hand-grip strength and, Role-physical, Role-emotional and Social functioning domains of Short form-36. 6-minute walk distance was negatively correlated with timed up and go. SF-physical functioning was positively correlated with hand-grip strength, Medical Research Council-sumscore and 5 repetition-chair-stand. SF-general health was positively correlated with hand-grip strength.

Conclusion: There were varying degrees of functional impairment in survivors. Therefore, it could add advantage to assess these patients after nearly 4-6 weeks following discharge in order to ascertain rehabilitation needs and giving appropriate therapies.

Keywords: post-intensive care syndrome, COVID-19, functional capacity, six-minute walk test, handgrip strength, chair stand test

Condensed Abstract: Acute respiratory distress syndrome survivors related to COVID-19 demonstrated impairments in 6-minute walk test, 5 repetition-chair-stand test, hand-grip strength and, some domains of Short form-36. In order to ascertain rehabilitation needs and giving appropriate therapies, assessing these patients after nearly 4-6 weeks following discharge could add an advantage.

Özet

Amaç: Bu retrospektif çalışmanın amacı, COVID-19 geçiren hastalarda fonksiyonel kapasiteyi, global kas zayıflığını ve yaşam kalitesini belirlemektir.

Arka plan: Akut solunum sıkıntısı sendromu sonrası sıklıkla fiziksel fonksiyonda, yaşam kalitesinde bozulma ve kas güçsüzlüğü gelişir.

Method: COVID-19 ile ilişkili akut solunum sıkıntısı sendromu sonrası taburcu olduktan 4-6 hafta sonra Fiziksel Tıp ve Rehabilitasyon Polikliniği'nde standart fiziksel klinik değerlendirme, Medical Research Council-toplam puan, el kavrama kuvveti, 6 dakika yürüme testi, 5 defa oturup kalkma testi, zamanlı kalk ve yürü testi ve Kısa form-36 testi uygulandı.

Bulgular: Ortanca yaşı 69 olan ve yoğun bakımda kalış süresi 10 gün olan 15 hasta (10 erkek, 5 kadın) analiz edildi. Kısa form-36, 6 dakika yürüme testi, 5 defa oturup kalkma testi, el kavrama kuvveti ve fiziksel, duygusal ve sosyal işlevsellik alanlarında bozulmalar vardı. 6 dakikalık yürüme mesafesi, zamanlı kalk ve yürü testi ile negatif yönde ilişkiliydi. Kısa form-fiziksel fonksiyon, el kavrama kuvveti, Medical Research Council-toplam puanı ve 5 defa oturup kalkma testi ile pozitif yönde ilişkiliydi. Kısa form-genel sağlık durumu el kavrama kuvvetiyle pozitif yönde ilişkiliydi.

Sonuç: COVID-19'a bağlı akut solunum sıkıntısı sonrası yoğun bakım ünitesinden taburcu olanlarda değişen derecelerde fonksiyonel bozulma vardı. Bu nedenle bu hastaların taburculuktan yaklaşık 4-6 hafta sonra değerlendirilmesi, rehabilitasyon ihtiyaçlarının belirlenmesi ve uygun tedavilerin verilmesi açısından avantaj sağlayabilir.

Introduction

COVID-19 virus that emerged in 2019 could cause Acute Respiratory Distress Syndrome (ARDS) which requires intensive care and respiratory support (1). After recovery from acute critical illness and discharge from hospital, disabilities related to Post intensive care syndrome (PICS) could impact one's life. PICS includes Intensive Care Syndrome Acquired Weakness (ICUAW), neuromyopathies, deconditioning, pulmonary dysfunction, cognitive and mental dysfunction, and might reduce functional capacity and health related quality of life (HRQoL) (2).

The long-term consequences of COVID-19 are unclear. There is limited data and information about the functional capacity of these patients after hospital discharge despite increasing the number of articles published about symptoms, diagnosis, preventions, supportive managements and short-term complications (1).

Previous studies in ARDS related to Severe Acute Respiratory Syndrome (SARS) have demonstrated significant impairment in lung function, exercise capacity measured by Six-minute walk test (6MWT) and HRQoL measured by Short Form-36 (SF-36) in short and long term (3). In COVID-19, patients had lower functional capacity measured via 6MWT after achieving hemodynamic stability following ICU discharge in hospital and just after hospital discharge (4,5). In an inpatient rehabilitation unit following ICU stay, only 45% of post-acute COVID-19 patients were able to walk, 18% of them were feasible for 6MWT and the distance was 45±100 meter (6).

Follow-up evaluation of COVID-19 patients after hospital discharge might help assessing and managing the symptoms of PICS, functional capacity and need for physical therapy. European Respiratory Society and American Thoracic Society recommends an assessment at 6-8 weeks following discharge in COVID-19 patients for the rehabilitation need (7).

The aim of this cross-sectional study is to demonstrate the functional capacity, global muscle weakness and HRQoL in COVID-19 survivors after 4-6 weeks following hospital discharge.

Materials and Methods

The STROBE checklist was followed. This cross-sectional, descriptive study was approved by Medical Ethics Committee (Koc University) before the study and registered to ClinicalTrials.gov (NCT04952844). COVID-19 related ARDS survivors were assessed 4-6 weeks following discharge from the hospital in Koc University Hospital, Physical Medicine and Rehabilitation Department outpatient clinic between June 2020 and September 2020. All ARDS survivors related to COVID-19 who were treated in ICU were invited to outpatient clinic after 4-6 weeks following discharge from hospital in order to assess the need of rehabilitation. 15 patients out of 32 attended the evaluation.

Inclusion criteria were as follows; older than 18 years, ARDS survivors related to COVID-19 who were treated in ICU and attended the outpatient evaluation. Exclusion criteria were as follows; diseases that could affect functional capacity, muscle strength and quality of life, such as cancer, spinal cord disease, neuromuscular diseases and unwillingness to attend the study.

The primary outcome was 6MWT. Secondary outcomes were Medical Research Council (MRC)-sumscore, hand-grip strength (HGS), 5 repetition sit-to-stand test (5STS), timed up and go test (TUG) and Short form-36 (SF-36).

Six-minute walk test is a field test evaluating submaximal aerobic capacity. The technical standards are defined by European Respiratory Society and American Thoracic Society. The individuals were asked to walk as far as possible in a 30-meter corridor in 6 minutes and the distance, oxygen saturation (SpO2), heart rate, systolic blood pressure and Borg rate of perceived exertion (RPE) scale (0-20) were recorded before and immediately after the test, and at the first-minute of recovery. It is a valid and responsive measurement of functional capacity and also predicts HRQoL in ARDS survivors with minimal clinical important difference of 20-30 meters (8). Mean 6MWD of healthy individuals aged 50-85 was defined as 631 ± 93 m (ranging 383-820 m); it was 84 m greater in male compared to female subjects (9).

Handgrip strength was measured using a handheld dynamometer (JAMAR Plus+ electronic dynamometer, part number: 563213, serial number: 2019070814, Sutton-in-Ashfield, Nottinghamshire, UK) according to the instructions of the American Society of Hand Therapists. Patients were requested to seat placing their arms by their sides with the elbow flexed to 90°, the forearm mid-prone, and the wrist in neutral position. Using standard verbal encouragement, patients were asked to grip the dynamometer in dominant hand with maximal effort. Three trials were performed with a 30-second interval between trials and the highest value was recorded in kg. The cut-off values of grip strength are 28.6 kg and 16.4 kg in elderly men and women, respectively. (10). It correlates with 6MWD in subjects with chronic obstructive pulmonary disease exacerbation (11).

Medical Research Council-sumscore which is valid and reliable tool in survivors of critical illness, were used in order to evaluate the overall muscle strength (12). Muscle strength of arm abduction, forearm flexion,

wrist extension, hip flexion, knee extension and ankle dorsiflexion in both limbs were evaluated and graded using MRC scale that range from 0 (no muscle contraction) to 5 points (normal muscle strength). Clinical important muscle weakness is defined as MRC-sumscore <48 out of maximum 60 points (13).

For HRQoL in ARDS survivors, SF-36 was used. Reductions in all domains were demonstrated in ARDS (14). It is a self-reported survey which evaluates individual health status with eight parameters (physical function, pain, role limitations attributed to physical problems, role limitations attributed to emotional problems, mental health, social functioning, energy/vitality, general health perception). There is not a sum score, each section is scored between 0-100, 0 indicates the worst condition, 100 indicates the best.

5 repetition sit-to-stand test was performed to evaluate the strength and endurance of lower limbs. Patients were asked to sit on a chair with 46 cm seat height by crossing their hands over their chest and stand and sit five times consecutively as fast as possible. The test starts in the sitting position and terminate at the end of fifth sitting and the time was recorded (15). Heart rate and SpO2 were monitorised during the test. The mean time of 5STS test was 14.1 sec in COPD patients with mean age 69 years (16). Normative values of the 5-repetition sit to stand test are 11.4 sec (60 to 69 years), 12.6 sec (70 to 79 years), and 14.8 sec (80 to 89 years) in healthy individuals. It could be considered worse than average performance if exceed these values (17). The 5STS test is a significant clinical determinant of poor performance in COPD if ≥ 13 seconds (18).

Timed up and go test was used to assess physical function. It is an objective, reliable and simple test to evaluate both balance and functional movement. The patients were asked to get up from a chair, walk 3 m, turn around, walk back and sit on the chair again. The time was recorded in seconds (19). Normative TUG values for healthy elderly were described as 8.1 (7.1-9.0) sec for 60 – 69 years, 9.2 (8.2-10.2) sec for 70–79 years, and 11.3 (10.0-12.7) sec for 80–99 years. It could be decided worse if time exceeds the upper limits (20).

Statistical analysis was performed using the SPSS Version 26 for Windows. Shapiro-Wilk test was used for normal distribution. Demographic variables were analyzed with descriptive statistics and presented as median (min-max) (interquartile range: IQR) or number (percentage). The correlation between the variables was analyzed using Spearman's correlation test. Statistical significance level was accepted as $p < 0.05$.

Results

Fifteen patients (10 men, 5 women) out of 25 were assessed by a Physical Medicine and Rehabilitation physician at the 4-6 weeks following discharge from hospital. The characteristics of the patients were presented in Table 1.

TABLE 1: Demographic and clinical characteristics of COVID-19 survivors.

Variables	Value Median (Interquartile range) / Number
Age (years)	69 (59-75)
Sex (man/woman)	10/5
BMI (kg/m2)	27.7 (26.0-32.3)
BMI, man (kg/m2)	26.8 (25.6-31.7)
BMI, woman (kg/m2)	30.5 (27.4-34.7)
Length of ICU stay (day)	10 (7-18)
Length of total hospital stay (day)	21 (16-25)
Length of mechanical ventilation (day)	5 (0-15)
Comorbidities (n, %)	
Hypertension	9 (60%)
COPD	2 (13%)
Diabetes mellitus	5 (33%)
Oxygen need following discharge (n, %)	1 (7%)

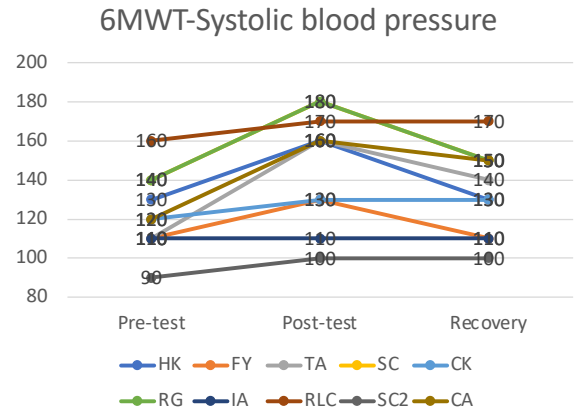
BMI: Body mass index; ICU: Intensive care unit; COPD: Chronic Obstructive Pulmonary Disease

Ten patients completed the 6MWT, three were unable to perform the test due to dyspnea (n=2) or hypertension (n=1) and two refused to attend the test. Median 6MWD was 387 m (min-max: 210-540 m, IQR: 284-480 m). SpO2, heart rate, systolic blood pressure and Borg RPE scale before the test, immediately after the test and at first minute of recovery were presented in Figure 1.

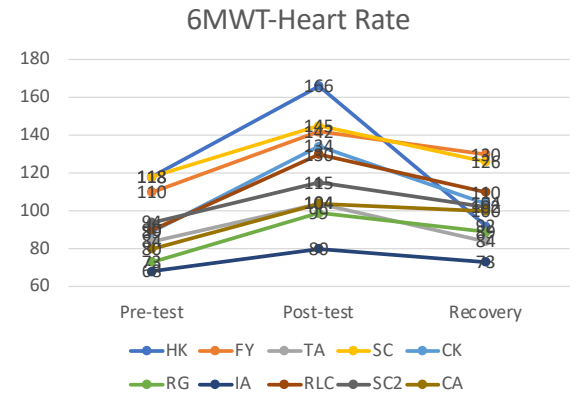
Figure Legends

Figure 1: Systolic blood pressure (a), heart rate (b), SpO2 (c) and Borg RPE (d) before the test, immediately after the test and at first minute of recovery for each individual patient (provided by the initials of the patient name). RPE: Rate of perceived exertion

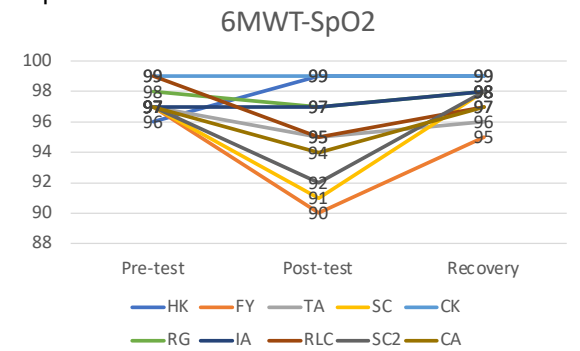
1a: Systolic blood pressure



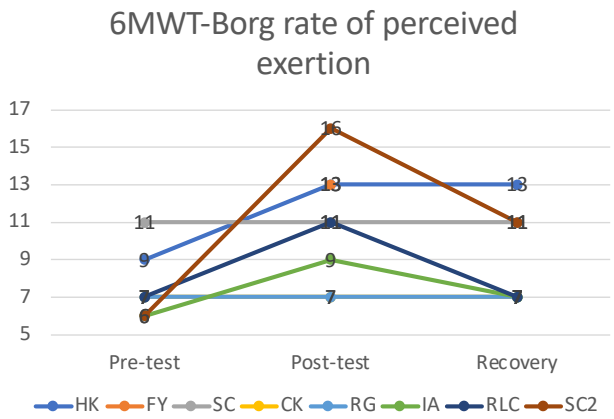
1b: Heart rate



1c: SpO2



1d: Borg RPE



6MWD was significantly negatively correlated with TUG and age (rs(7)= -.916, p=0.001 and rs(8)= -.673, p=0.033, respectively). Male patients walked longer distance than the females (421m / 345m).

All patients could perform the HGS test. Median HGS was 24 kg (min-max: 6-36 kg, IQR: 12-30 kg) in all patients, 26.5 kg (min-max: 12-36, IQR: 21.3-32) in men and 9 kg (min-max: 6-27, IQR: 6.5-20.5) in women. 50% of men and 80% of women had HGS values lower than the aforementioned cut-off values. HGS was significantly correlated with physical functioning, social functioning and general health domains of SF-36 (rs(13)= .711, p=0.003, rs(13)= .516, p=0.049 and rs(13)= .751, p=0.001, respectively).

Motor strength was evaluated in all patients. Median score was 57 (min-max: 48-60, IQR: 51-60) in all patients, 57.5 (min-max: 48-60, IQR: 51.5-60.0) in men and 56 (min-max: 48-60, IQR: 49.5-60) in women. MRC-sumscore was significantly positive correlated with physical functioning and role-physical domains of SF-36 (rs(13)= .709, p=0.003 and rs(13)= .539, p=0.038, respectively).

Twelve patients were able to complete the TUG test (2 women who also could not perform the 6MWT, could not perform TUG test due to dyspnea, 1 man did not want to attend the test). Median time was 7.6 sec (min-max: 6.4-24.7, IQR: 6.9-9.1). There was a significant negative correlation between TUG and 6MWD (rs(7)= -.916, p=0.001). TUG was normal in all patients except one man (24.7 sec).

Twelve patients completed the test, 2 women who also could not perform either 6MWT or TUG tests, could not perform 5STS test due to dyspnea, 1 man who also could not perform the 6MWT could not perform due to hypertension. Median time was 14.4 sec (min-max: 9.0-19.3, IQR: 13.1-16.3). There was a significant negative correlation between 5STS and SF- physical functioning (rs(10)= -.577, p=0.05).

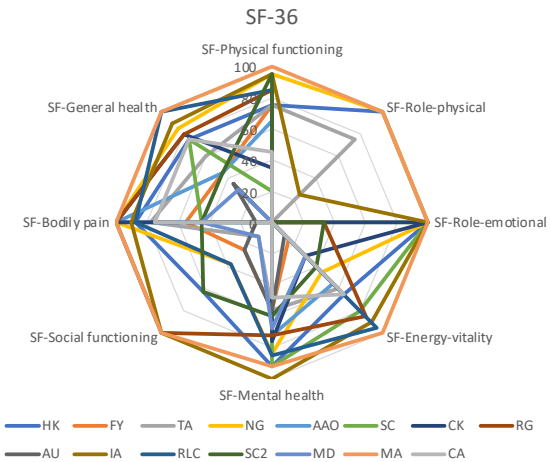
All patients completed the SF-36. There were impairments in role-physical, role-emotional, social functioning domains of SF-36 (Table 2).

TABLE 1: Median values of SF-36 domains of COVID-19 survivors.

SF-36	Value Median (min-max) (Interquartile range)
Physical functioning	75 (0-100) (35-95)
Role-physical	0 (0-100) (0-75)
Role-emotional	33.3 (0-100) (0-100)
Energy-vitality	60 (11.2-100) (30-85)
Mental health	72 (48-100) (56-92)
Social functioning	25 (10-100) (0-62.5)
Bodily pain	87.5 (30-100) (45-100)
General health	75 (30-100) (45-85)

SF-36 scores of the 15 patients were represented in Figure 2.

Figure 2: Short Form-36 scores of 15 patients



SF- physical functioning was negatively correlated with 5STS (rs(13)= -.577, p=0.05), and positively correlated with MRC-sumscore and HGS (rs(13)= .709, p=0.003 and rs(13)= .711, p=0.003, respectively). There was significant positive correlation between SF- Role-physical and MRC-sumscore (rs(13)= .539, p=0.038). There was significant positive correlation between SF- Social functioning and HGS (rs(13)= .516, p=0.049). There was significant positive correlation between SF- General health and HGS (rs(13)= .751, p=0.001). SF-36 items had not any correlations with 6MWD or TUG.

Discussion

This study demonstrated that following 4-6 weeks from hospital discharge COVID-19 related ARDS survivors had lower median 6MWD than normal population. Oxygen saturation was decreased at the end of the test and returned to normal at the recovery period in three out of 10 patients who could perform the test. 6MWD was not correlated with HGS, MRC-sumscore, 5STS or SF-36, however it was negatively correlated with TUG.

At 4-6 weeks following discharge, patients had lower median HGS and longer median 5STS, however median MRC-sumscore, TUG and SF-36 except for three domains was normal. Lower HGS was correlated with poor quality of life in physical functioning, social functioning and general health domains of SF-36. Longer 5STS time was associated with worse physical functioning scores in SF-36.

The median 6MWD was lower than the normal population in our patients. In healthy subjects ages between 45 and 85 years, the mean 6MWD were 682 m and 643 m for men and women, respectively (21). In patients with COPD <350 m was associated with increased mortality and morbidity (22) . A meta-analysis in critical illness survivors reported that ARDS patients had 73 meters shorter 6MWD than that of non- ARDS patients at 3, 6 and 12 months, and the difference was stable at these time points. In ARDS patients 6MWD improved from 361 m at 3 months to 436 m at 12 months (23). In our patients who attended the test, 6MWD was lower than 300 m in 6 patients (3 patients could not even start the test due to dyspnea and high systolic blood pressure). In that meta-analysis male sex was significantly associated with greater 6MWD and comorbidities prior to ICU was associated to lower 6MWD, and there was no association between 6MWD and ICU related factors such as illness severity, neuromuscular blockers, corticosteroids, mechanical ventilation duration, length of ICU or hospital stay (23). Similarly, in our study, male patients walked longer distance than the females, patients with more than one comorbidity walked shorter distance or could not perform the test, and ICU related factors did not affect the walking distance. In our study, 66% of the patients were able to perform 6MWT which is higher than that of Curci et al. (19%) which evaluated COVID-19 patients at early post-acute period. 6MWD in our study (387 m) was also longer than theirs (45 meters) (24). 6MWT is not feasible due to dyspnea which is present even in minimal activities in the early post-acute period, as European Respiratory Society and American Thoracic Society recommend assessment at 6-8 weeks following discharge (7). On the other hand, Spielmanns et al reported that 6MWD was 176±141 meters in COVID-19 patients following acute care phase of the infection, measured within two days after hemodynamical stability, and 357±132 meters after a 3-week pulmonary rehabilitation program (5). In another study, 6MWT was performed in 26 discharge-ready COVID-19 patients in order to investigate silent hypoxia, it was reported that 50% of the patients completed the test, the other half terminated prematurely due to hypoxia (SpO2<90%). The comorbidities were similar between them, but history of ICU and mechanical ventilation were higher in early terminated group (25). We also observed desaturation in 3 patients at the end of the test which improved in the first minute of recovery. They concluded that 6MWT is a potential tool in the diagnosis of asymptomatic exercise-induced hypoxia in COVID-19 patients prior to hospital discharge.

Following hospital discharge, 6MWD was measured 162±72 meters in elderly patients with COVID-19 (4), but the time period after discharge was not given. In another study with 97 SARS survivors (31 required ICU admission, 6 required invasive mechanical ventilation), 6MWD was also lower than normal subjects (464 m, 502 m and 511 m at 3, 6 and 12 months after symptom onset, respectively). ICU support or intubation were not found to affect 6MWD at 12 months (26). They found 6MWD was correlated with SF-36 except for mental health domain at 12 months. Contrarily there was no correlation between 6MWD and any SF-36 domains in our patients. Small sample size and earlier evaluation time in our sample might have masked the association.

To assess functional capacity 6MWT is the most widely used test, however it is not a feasible test to perform for all patients who recently achieve stability. Therefore, easier tests might be more convenient and informative in the early period (27). The TUG assesses mobility skill, strength, balance, and agility in many populations and conditions (28). In our study, 6MWD was negatively correlated with TUG. This strong correlation makes us suggest that TUG might reflect functional capacity in this population during 4-6 weeks after hospital discharge and it might be an alternative test to 6MWT in patients who are unable to perform 6MWT.

Another alternative test might be for functional capacity assessment in severely deconditioned patients. 5STS correlates with exercise capacity and lower limb strength in COPD (16).

In pulmonary fibrosis there was moderate correlation between 5STS and 6MWD (28). However, there was not such a correlation in COVID-19 related ARDS in our patients. All patients in our study except one had longer 5STS than normal individuals. The test represents sitting and standing in the daily life that exhibit lower extremity strength. It could give information about mild deficits in quadriceps that we could not assess with manual muscle test in PICS. 5STS can be used during each phase of the disease whenever COVID-19 patients are able to stand and sit independently. On the other hand, in our study the patients who could not perform 6MWT also could not perform 5STS.

To assess muscle strength HGS and MRC are easy to perform and feasible tests as all patients in our study could perform both measures. HGS was low in 2/3 of our COVID-19 survivors similar to two studies regarding SARS survivors measured at 6 weeks (29). As HGS is a measure of general health, it was recommended for the patients that could not perform 6MWT during the exacerbation period due to its moderate correlation (11). However, we could not detect similar correlation in COVID-19 survivors. MRC-sumscore was above the cut-off value in our population. MRC-sumscore could not determine those patients who could not perform 5STS and low HGS values in 4-6 weeks. So, in addition to manual muscle test, using performance tests are recommended. MRC-sumscore maybe more useful in early period in order to screen the change in muscle strength.

It is reported that, HRQoL is affected in COVID-19 after hospital discharge (4). SF-social functioning was worse in these patients, but this might not be unique for post ARDS patients, pandemic also could affect negatively social functioning of healthy individual. There were problems with work or other daily activities as a result of physical and emotional health in COVID-19 related ARDS survivors. Interestingly there was not significant impairments in other parameters of SF-36. This might be due to the gratitude recovering from a mortal disease and trusting their doctors about their health. Quality of life was worsened 44% of patients measured by EuroQol visual analogue scale in 143 patients (15% received non-invasive ventilation; 5% received invasive ventilation) 60 days after the onset of COVID-19 symptoms in the post-acute outpatient service (30). We only included COVID-19 patients required ICU.

The limitations of the study as follows: The sample size of the cohort is small; however, we analyzed the patients and results in detail and this study might shed light to future studies and professionals involved in the management of patients with COVID-19. There are no long-term follow-up results of the same patients, because the patients did want to come hospital again, only one of them attend to tele-rehabilitation program. Strengths of the study as follows: This study demonstrates the functional capacity, disability and overall muscle strength of COVID-19 survivors 4-6 weeks after discharge in detail. It could shed light to clinical practice and future scientific researches.

In conclusion COVID-19 related ARDS survivors at 4-6 weeks after hospital discharge had negative results in 6MWT, 5STS, HGS, and several domains of SF-36. 6MWD was negatively correlated with TUG. There are varying degrees of functional impairment in survivors. So, it could add advantage to assess the patients after nearly 4-6 weeks following discharge in order to ascertain rehabilitation needs. Furthermore, this documentation is beneficial both for clinical practice and scientific research. Middle and long-term consequences should be detected with long term studies in order to provide appropriate management.

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