Original Article

Long-term COVID-19 effects on pulmonary function, exercise capacity, and health status

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Submission: 19-02-2021
Accepted: 08-04-2021
Published: 14-01-2022

Abstract:

BACKGROUND: The long-term effects of respiratory function and related physiological characteristics of coronavirus disease 2019 (COVID-19) survivors have not yet been studied in depth.

OBJECTIVE: To examine pulmonary function, exercise capacity, and health-related quality of life among COVID-19 survivors.

METHODS: Eighty-five survivors with confirmed COVID-19 were evaluated at the end of 3 and 6 months after disease onset. The assessment included lung function, diffusing capacity, 6-min walk distance (6MWD), and health status by the 36-item Short-Form General Health Survey (SF-36) questionnaire.

RESULTS: Totally 85 survivors, 48 (56.5%) were men. The mean (standard deviation) age was 34.6 (9.9) years. Thirteen patients (15.2%) had medical co-morbidities the mean length of hospitalization was 18.5 (5.6) days. 25 (29.4%) required intensive care unit admission, whereas 6 (7%) of them required invasive mechanical ventilation. No significant differences were observed between lung volume parameters. At 6 months, there was a significant reduction in diffusing capacity for carbon monoxide (DLCO), $P = 0.02$*. 25 (29.4%) of patients had impaired DLCO $\leq$80% predicted. Regarding 6MWD, a significant increase was noted in 6MWD from 486 ± 72 m at 3 months to 526 ± 82 m at 6 months ($P = 0.001$*). The 6MWD was lower than that for normal controls of the same age groups. There was significant impairment of health status assessed by SF-36 questionnaire among COVID-19 survivors at 6 months as compared with controls of the same age groups. There were significant positive correlations between lung function parameters (FVC, VC, FEV1, and DlCO) with several SF-36 domains.

CONCLUSION: In discharged survivors with COVID-19, 23.5% had significant impairment of diffusion capacity abnormality of lung function. The exercise capacity and health status were considerably lower than that of a normal population after 6 months postinfection.

Keywords:

COVID-19, exercise capacity, quality of life

Coronavirus disease 2019 (COVID-19) is considered a public health crisis caused by a novel coronavirus, known as severe acute respiratory syndrome (SARS) coronavirus 2. COVID-19 first appeared in Wuhan, China, in early 2019, then broke out in China and spread worldwide.[1]

The virus was transmitted to humans through inhalation or contact with infected droplets with an incubation period ranges from 2 to 14 days. The global impact of this epidemic has gained attention with extensive measures to effectively control the outbreak. As a new infectious disease-carrying adverse outcomes and high risk of severe course and intensive care unit (ICU) admission, it is necessary to

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.atm_82_21

How to cite this article: Magdy DM, Metwally A, Tawab DA, Hassan SA, Makboul M, Farghaly S. Long-term COVID-19 effects on pulmonary function, exercise capacity, and health status. Ann Thorac Med 2022;17:28-36.

explore COVID-19 clinical characteristics, which may help to manage properly its sequelae in the post-acute phase.[2]

According to recent reports, lung computed tomography (CT) imaging is an essential modality for early detection of lung abnormalities related to COVID-19 pneumonia and useful for monitoring the rapid progression of lung injury.

Researchers revealed that discharged patients with COVID-19 pneumonia are still having residual abnormalities in chest CT scans; patchy ground-glass appearance and interstitial thickening are common CT features reported with longer time from the onset of the symptom; denoting interstitial edema and alveolar exudation resulting in pulmonary fibrosis.[3]

Many studies have shown that patients who survived SARS, have reported persistent abnormalities during prospective follow-up; lasting for months or even years.[4-6] A longitudinal 1-year follow-up of survivors of severe illness reported residual abnormalities detected with pulmonary function testing with impairment in diffusing capacity for carbon monoxide (DLCO) during the first 6 months after recovery. Furthermore, impairment in Health-related quality of life (HRQoL) was reported in SARS survivors.[5,6]

Although it has been reported that short-term radiological outcomes and abnormal lung function found in patients when discharged from the hospitals, the long-time follow-up of COVID-19 survivors have not been reported yet.

Therefore, we aimed to describe the long-term impact of COVID-19 on pulmonary function, exercise capacity, and quality of life among survivors.

Methods

Patient selection

This prospective follow-up study on COVID-19 survivors after discharge from the hospital from March to December 2020. A total of 85 COVID-19 patients were admitted to Assiut University Hospital.

Eligible patients met the following criteria: (1) had laboratory-confirmed COVID-19 (by real-time reverse transcription-polymerase chain reaction); (2) aged ≥18 years.

We excluded (1) subjects with incomplete information on the quality of life survey; (2) patients who were not able to complete the interview; and (3) patients with a previous history of pulmonary resection, neurological disorder, or mental illness.

We obtained written informed consent from all patients. This prospective outcome study of COVID-19 survivors was approved by the ethics committee of Assiut University Hospital.

Assessment

Patient clinical history, body mass index, smoking habit, laboratory panel (lactate dehydrogenase; C-reactive protein; D-dimer), and setting transitions were collected.

All patients were evaluated in the pulmonary function laboratory at the end of 3 and 6 months after disease onset. During the visit, patients were interviewed and underwent a physical examination, pulmonary function testing, and a standardized 6-min walk distance (6MWD).[7] Furthermore, they completed the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) to measure health status.[8]

Six-minute walk distance

6MWD provides a useful assessment tool of cardiopulmonary and musculoskeletal function that is relevant to daily activities.[9,10] The recorded results of 6MWD were compared with the normative reference data collected from a survey on 538 normal healthy population.[11] For analysis, the 6MWD data stratified into age groups ([20–30], [31–40], [41–50], [>50] years).

Pulmonary function tests

Resting pulmonary function tests were performed for all patients. Spirometric parameters and lung volumes were measured using (Zan 300; Sensor Medics MGA USB, Oberthulba, Germany).[12]

DLCO adjusted for hemoglobin (DLCO) and carbon monoxide transfer coefficient [KCO]) was determined by the single-breath technique (Zan 300; Sensor Medics MGA USB, Oberthulba, Germany) and categorized according to severity as recommended.[13]

All laboratory staff members wore personal protective equipment; including N95 respirators, protective goggles, gloves, and gowns. In addition, a disposable filter (Spiroguard 2800/01, USA) was used for each patient.

36-Item Short Form Survey

The (SF-36) is a self-reported questionnaire used for assessing HRQOL.[8] It comprises 36 questions which cover eight domains of health.

Physical health-related domains include general health (GH), physical functioning (PF), role physical (RP), and bodily pain (BP). Mental health-related scales include vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Each domain is

scored on a 0–100 metric scale, the higher score reflecting better health.

SF-36 is administered for all participants at 3- and 6-month visits. Scores from the eight domains recorded and analyzed. The results from SF-36 domain scores were stratified into two age groups (18–40 years and 41–64 years) for comparison with normative data collected from a random survey of Chinese adults.[14]

Computed tomography visual quantitative evaluation

All patients underwent high-resolution spiral CT (SOMATOM Definition Flash Siemens; Erlangen, Germany) scans in the supine position during the end of inspiration.

Images were reconstructed at 1 mm slice thickness, with 1 mm increment, 512 mm × 512 mm. The images were assessed by two radiologists.

The severity of pulmonary inflammation was based on summing up the acute inflammatory lesions involving each lobe; scored as 0 (0%), 1 (1%–25%), 2 (26%–50%), 3 (51%–75%), or 4 (76%–100%), respectively.

An overall lung "total severity score" (TSS) was reached by summing the five lobe scores (ranged from 0 to 20).[15,16]

Statistical analysis was performed using the Statistical Package for the Social Science version 16.0 (SPSS, version 16; SPSS Inc., Chicago, Illinois, USA).

Descriptive data were presented as mean ± standard deviation (SD) for continuous variables or number (%) for categorical ones. Paired data *t*-test was used when appropriate.

A $P < 0.05$ was considered statistically significant.

Results

Of the first 104 patients hospitalized with COVID-19 infection in March 2020, 6 (5.7%) died. Among the 98 survivors, 13 (13.2%) did not attend 6-month assessment. Therefore, 85 patients completed all assessments including the 6-month assessment.

In total, 85 COVID-19 patients were enrolled in this study [Table 1], 48 (56.5%) were men. The mean (SD) age was 34.6 (9.9) years. Thirteen patients (15.2%) had comorbidities which included; chronic obstructive pulmonary disease $n = 2$ (2.3%); asthma $n = 1$ (1.1%); ischemic heart disease $n = 1$ (1.1%); hypertension $n = 5$ (5.8%); diabetes mellitus $n = 4$ (4.7%). The mean length of stay in hospital was 18.5 (5.6) days.

Table 1: Demographics of coronavirus disease 2019 survivors (*n*=85)

	All (*n*=85)
Age (years)	34.6±9.9
Sex, *n* (%)	
Male	48 (56.5)
Female	37 (43.5)
BMI (kg/m^2)	24.6±3.8
Comorbidities, *n* (%)	13 (15.2)
COPD	2 (2.3)
Asthma	1 (1.1)
IHD	1 (1.1)
Hypertension	5 (5.8)
Diabetes mellitus	4 (4.7)
Smoking history, *n* (%)	
Active	12 (14.1)
Former	9 (10.5)
LOS in hospital (days)	18.5±5.6
ICU admission, *n* (%)	25 (29.4)
Mechanical ventilation, *n* (%)	6 (7)
Peak LDH level (U/L)	435.4±218.5
Peak CRP (mg/dl)	87.1±71.5
D-dimer (mg/L)	0.30±0.01
Total steroid dose (in terms of hydrocortisone, mg)[#]	10,805.6±11 449.4
Total severity score of CT scan	4.38±4.12
Total severity score of CT scan on the 14th day after discharge	2.85±1.43

[#]Cumulative steroid dosage during inpatient treatment and outpatient follow up was converted into hydrocortisone (mg) to facilitate analysis of the study. Data presented as mean±SD or *n* (%). BMI=Body mass index, COPD=Chronic obstructive pulmonary disease, IHD=Ischemic heart disease, LOS=length of stay, LDH=Lactate dehydrogenase, CRP=C-reactive protein, ICU=Intensive care unit, CT=Computed tomography, SD=Standard deviation

Among the 85 patients, 25 patients (29.4%) required ICU admission, whereas 6 patients (7%) needed invasive mechanical ventilation. At the acute phase, the TSS as determined by CT chest was 4.38 (4.12).

Lung function test results for COVID-19 survivors are shown in Table 2.

No statistically significant differences were noted between lung volume parameters at 3 and 6 months. A significant reduction was observed in DLCO after 6 months $P = 0.02$*, whereas there was an increase in KCO over the study period of 6 months ($P = 0.001$*).

The frequency of COVID-19 survivors with lung function parameters >80% of predicted values is as follows: at 3 months, forced expiratory volume in 1 s (FEV1) ($n = 3$; 3.5%), forced vital capacity (FVC) ($n = 6$; 7%), VC ($n = 6$; 7%), total lung capacity (TLC) ($n = 7$; 8.2%), DLCO ($n = 16$; 18.8%), and KCO ($n = 4$; 4.7%). Whereas at 6 months follow-up, FEV1 ($n = 4$; 4.7%), FVC ($n = 4$; 4.7%), VC ($n = 4$; 4.7%), TLC ($n = 3$; 3.5%), DLCO ($n = 25$; 29.4%), and KCO ($n = 3$; 3.5%).

Thus, there were 25 patients (29.4%) with impaired DLCO, whereas up to 4.7% of patients had a reduction in parameters of lung volume at 6 months [Table 3].

Six-minute walk distance

The 6MWD of the COVID-19 survivors at 3 and 6 months, compared with normative data is presented in Table 4. The mean 6MWD increased significantly from 486 ± 72 m at 3 months to 526 ± 82 m at 6 months (P = 0.001*).

Patients were stratified into different age groups and compared with the corresponding normative values; it was observed that exercise capacity was significantly lower than the normals [Table 4].

Determinants of six-minute walk distance

There were no significant associations between 6MWD and any of the following: Peak LDH, peak CRP, D-dimer, admission to ICU, FEV1%, FVC%, at 6 months post COVID-19 infection.

Whereas, longer hospital stay and total steroid dose, TSS, DLCO% were independent factors associated with lower 6MWD at 6 months [Table 5].

Table 2: Results of serial pulmonary function tests among coronavirus disease 2019 survivors (*n*=85)

	(% predicted)		*P*
	3 months	6 months	
FVC	102.5±13	102.4±14	0.321
FEV_1	107.0±12.4	106.0±13.3	0.23
TLC	104.5±16.5	105.0±18.1	0.42
VC	104.0±13.3	104.2±14	0.26
RV	106.3±46.2	110.4±45.2	0.43
DLCO	98.2±14.2	92.2±12.3	0.02*
KCO	107.1±14.6	115.5±13.6	0.001*

*Significant difference. Data are expressed as mean±SD. FVC=Forced vital capacity, FEV_1=Forced expiratory volume in 1 s, TLC=Total lung capacity, VC=Vital capacity, RV=Residual volume, DLCO=Diffusing capacity for carbon monoxide, KCO=Transfer coefficient (transfer factor per alveolar volume), SD=Standard deviation

Table 3: The frequency of coronavirus disease 2019 survivors with lung function parameters <80% of predicted values (*n*=85)

	n<80% predicted value (%)	
	3 months	6 months
FVC	6±7	4±4.7
FEV_1	3±3.5	4±4.4
TLC	7±8.2	3±3.5
VC	6±7	4±4.7
RV	6±7	4±4.7
DLCO	16±18.8	25±29.4*
KCO	4±4.7	3±3.5

*= significance. Data are expressed as mean±SD. FVC=Forced vital capacity, FEV_1=Forced expiratory volume in 1 s, TLC=Total lung capacity, VC=Vital capacity, RV=Residual volume, DLCO=Diffusing capacity for carbon monoxide, KCO=Transfer coefficient (transfer factor per alveolar volume), SD=Standard deviation

On comparing pulmonary function tests and 6MWD of patients requiring ICU admission with those who treated on medical wards Table 6; the lung function tests at 6 months showed significantly lower FVC, VC, TLC, and DLCO in survivors who had required ICU support than those who were treated onwards.

Health status score assessment

SF-36 domain scores at 3 and 6 months after illness onset in patients in whom did or did not require ICU support showed a significant impairment in quality of life as compared to the control group of the same age groups Tables 7 and 8.

There were significant positive correlations between lung function parameters (FVC, VC, FEV1, and DLCO) with several SF-36 domains (PF, RP, GH, SF, and RE). Furthermore, 6MWD had significant positive correlations with all SF-36 domains [Table 9].

Discussion

This prospective cohort study has shown that most of the COVID-19 survivors had relatively well-preserved lung function at 6 months after symptom onset. Whereas 29.4% of them had persistent impairment in DLCO with well-preserved KCO.

The overall pattern of lung function impairment in our study suggesting an increase in the intra-alveolar diffusion pathway which may be the result of diffuse alveolar destruction and capillary damage in the acute stage, followed by post-inflammatory changes such as atelectasis, ongoing alveolitis, and parenchymal fibrosis later in the course of the disease.[17]

As was the case previously with the SARS, revealed that recovered patients can be left with damaged lungs and ventilatory impairment defect was a common feature; that could last for months or even years.[6,18,19] Meo *et al*. reported that SARS and COVID-19 had similar biological and clinical characteristics.[20] In the follow-up studies on SARS survivors, revealed that impaired DLCO was the most common abnormality, ranging from 15.5% to 43.6%, followed by defective TLC, ranging from 5.2% to 10.9%.[6,18,19]

Another study by Park *et al*. showed that 37% of MERS survivors still presented with impairment of DLCO, but normal TLC, at 12 months follow-up.[21] Our results seem to be more consistent with the findings in SARS. Interestingly, in our study, the greater decline in DLCO versus DLCO/VA suggests that the diffusion membrane may be more causative of the pulmonary dysfunction compared to lowered lung volume. Whether COVID-19 survivors with impairment of DLCO or residual

Table 4: Six-minute walking distance among coronavirus disease 2019 survivors (*n*=85) at 3 and 6 months after the onset of illness compared with normative data

Outcome	Normal	After 3 months	After 6 months	*P*
All survivors (*n*=85), mean±SD		486±72	526±82	0.001*
Age groups (years)				
20-30 (*n*=25)				
Men (*n*=12)				
Mean±SD	652±102	478±68	559±83	0.001*
Mean difference (95% CI)		−174 (−198-−126)	−93 (−120-−55)**	
Women (*n*=13)				
Mean±SD	600±80	462±71	490±86	0.001*
Mean difference (95% CI)		−138 (−170-−80)	−110 (−140-−60)**	
31-40 (*n*=35)				
Men (*n*=20)				
Mean±SD	650±90	512±78	550±88	0.001*
Mean difference (95% CI)		−138 (−188-−90)	−100 (−140-−60)**	
Women (*n*=15)				
Mean±SD	615±85	470±66	492±80	0.001*
Mean difference (95% CI)		−145 (−195-−95)	−123 (−152-−80)**	
41-50 (*n*=16)				
Men (*n*=10)				
Mean±SD	620±70	470±65	530±73	0.001*
Mean difference (95% CI)		−150 (−192-−87)	−90 (−142-−43)**	
Women (*n*=6)				
Mean (SD)	520±60	402±72	462±78	0.001*
Mean difference (95% CI)		−118 (−155-−64)	−58 (−112-−30)**	
>50 (*n*=9)				
Men (*n*=6)				
Mean±SD	580±64	410±82	464±82	0.001*
Mean difference (95% CI)		−170 (−210-−90)	−116 (− 165-−85)	
Women (*n*=3)				
Mean±SD	535±72	399±94	377±88	0.001*
Mean difference (95% CI)		−136 (−180-−96)	−158 (−210-−90)**	

*= significance. SD=Standard deviation, CI=Confidence interval

Table 5: Multivariate analysis of predictors of six-minute walking distance at 6 months from symptom onset[a]

	OR (95%CI)	*P*
Peak LDH level (U/L)	7.14 (1.03-9.216)	0.046
Peak CRP (mg/dl)	2.12 (0.89-7.84)	0.251
D-dimer (mg/L)	1.23 (0.996-1.56)	0.025
Admission to ICU	3.21 (1.98-11.3)	0.321
Total steroid dose	3.31 (1.9-10.4)	0.001*
Length of hospital stay	0.89 (−1.21-5.76)	0.002*
Total severity score of CT scan on the 14th day after discharge	3.45 (1.09-8.92)	0.001*
FEV_1 (%)	1.23 (−4.8-20.6)	0.654
FVC (%)	0.91 (−1.76-22.76)	0.435
DLCO (%)	4.21 (1.5-9.98)	0.001*

*= significance, [a]Logistic regression analysis adjusted for age and sex. LDH=Lactate dehydrogenase, CRP=C-reactive protein, ICU=Intensive care unit, CT=Computed tomography, FVC=Forced vital capacity, FEV1=Forced expiratory volume in 1 s, DLCO=Diffusing capacity for carbon monoxide, CI=Confidence interval, OR=Odds ratio

abnormalities on chest CT will develop pulmonary fibrosis requires further investigation.

Similarly, Huang *et al*. investigated the influence of COVID-19 on lung function in the early convalescence phase. The authors reported impaired diffusing-capacity and lung imaging abnormalities in more than half of the patients.[22]

Also, Zhao *et al*. analyzed 55 patients who recovered from COVID-19 and found that after 3-month follow-up; abnormal CT findings and DLCO anomalies were still present.[23]

The lung function parameters (FVC, VC, TLC, RV), and DlCO percentage of predicted) in survivors who required ICU support were significantly lower than those of

Table 6: Comparison of lung function indices and six minute walking distance in coronavirus disease 2019 survivors who had required intensive care unit care (*n*=25) versus those treated on the wards (*n*=60)

	ICU/no ICU		*P*
	3 months	6 months	
FVC (% predicted)			
Mean±SD	93.5±14.0 versus 107.5±12.1	97.6±15.8 versus 106.8±13.5	4.1±1.7 versus−0.7±1.0
95% CI	7.9-19.2	1.5-15.2	−9.6-−2.1
P	−0.01*	−0.02*	−0.01*
FEV_1 (% predicted)			
Mean±SD	102.0±13.1 versus 111.1±14.7	103.8±12.7 versus 108.2±15.4	1.8±1.2 versus−2.9±1.3
95% CI	3.0-15.1	−1.8-10.6	−9.0-−0.4
P	−0.01*	−0.17	−0.03*
TLC (% predicted)			
Mean±SD	94.6±16.1 versus 110.3±16.4	98.2±19.3 versus 110.1±14.1	3.6±3.9 versus−0.2±1.9
95% CI	8.7-20.5	5.0-18.7	−11.6-4.0
P	−0.01*	−0.01*	−0.03*
VC (% predicted)			
Mean±SD	94.7±13.1 versus 107.9±12.5	98.4±16.4 versus 105.0±14.9	3.7±1.3 versus−2.8±1.5
95% CI	7.4-18.9	−0.9-14.1	−11.3-−1.9
P	−0.01*	−0.08	−0.01*
RV (% predicted)			
Mean±SD	96.7±39.4 versus 115.7±45.2	99.9±52.6 versus 118.6±32.2	3.2±12.3 versus 2.9±7.2
95% CI	−1.3-38.2	−2.4-36.7	−25.0-24.3
P	−0.06	−0.08	−0.78
DLCO (% predicted)			
Mean±SD	84.3±18.4 versus 101.3±12.4	87.7±22.3 versus 98.3±16.6	3.4±2.2 versus−2.9±1.6
95% CI	11.2-24.4	3.0-16.2	−11.9-−0.6
P	−0.01*	−0.01*	−0.03*
KCO (% predicted)			
Mean±SD	104.9±13.5 versus 107.4±13.7	109.4±15.3 versus 110.2±15.6	4.5±1.7 versus 2.6±1.6
95% CI	−3.4-8.2	−5.3-6.9	−6.5-2.7
P	−0.41	−0.83	−0.38
6MWD (m)			
Mean±SD	458.2±86.8 versus 466.4±80.7	519.7±101.4 versus 491.5±92.9	64.5±14.5 versus 25.1±9.7
95% CI	−27.1-42.5	−11.3-12.4	−74.9-−4.0
P	−0.64	−0.97	−0.03*

*Statistically significant. Values are shown as mean±SD ICU versus non-ICU with 95% CI of difference and *P* values. FVC=Forced vital capacity, FEV_1=Forced expiratory volume in 1 s, TLC=Total lung capacity, VC=Vital capacity, RV=Residual volume, DLCO=Diffusing capacity for carbon monoxide, KCO=Transfer coefficient (transfer factor per alveolar volume), SD=Standard deviation, 6MWD=Six minute walking distance, CI=Confidence interval, ICU=Intensive care unit

Table 7: Health-related quality of life (short form-36) among coronavirus disease 2019 survivors who required intensive care unit admission (*n*=25) at 3 and 6 months after illness onset in comparison with normative data

SF-36 domains/ age group (years)	Normal, mean±SD	3 months versus normal, mean±SD; mean difference (95% CI)	6 months versus normal, mean±SD; mean difference (95% CI)
PF			
18-40	96.3±6.6	80.4±12.6; −15.9 (−20.9-−7.4)*	89.5±10.0; −6.8 (−12.0-3.7)*
41-60	90.6±12.4	68.3±21.5; −22.3 (−36.0-−8.6)*	74.9±24.1; −15.7 (−25.8-−7.4)*
RP			
18-40	85.6±27.7	35.3±35.9; −50.3 (−73.7-−35.4)*	75.5±30.6; −10.1 (−20.2-4.3) (NS)
41-60	81.6±31.7	12.5±29.2; −69.1 (−88.4-−53.0)*	30.1±37.6; −51.5 (−70.4-−35.4)*
BP			
18-40	86.4±19.4	72.4±27.5; −14.0 (−20.5-−3.2)*	74.3±20.4; −12.1 (−18.9-−4.7)*
41-60	82.6±22.9	60.5±31.7; −22.1 (−34.5-2.3) (NS)	69.1±27.7; −13.5 (−24.6-−1.4)*
GH			
18-40	59.5±19.4	52.3±16.3; −7.2 (−14.7-5.9) (NS)	52.4±15.1; −7.1 (−14.2-1.3) (NS)
41-60	53.2±20.1	42.1±12.4; −11.1 (−20.4-5.3) (NS)	50.7±18.8; −2.5 (−12.1-5.1) (NS)

Contd...

Table 7: Contd...

SF-36 domains/ age group (years)	Normal, mean±SD	3 months versus normal, mean±SD; mean difference (95% CI)	6 months versus normal, mean±SD; mean difference (95% CI)
VT			
18-40	60.2±18.3	50.5±8.3; −9.7 (−12.0-−3.7)*	53.8±12.4; −6.4 (−12.4-−3.2)*
41-60	60.3±18.9	46.7±10.3;−13.7 (−20.3-−8.3)*	47.9±12.3; −12.4 (−20.3-−1.7)*
SF			
18-40	90.2±16.2	52.5±26.5; −37.7 (−46.5-−21.5)	75.2±15.4; −15.0 (−20.8-−5.6)*
41-60	92.4±16.5	58.3±25.2; −34.1 (−46.2-−16.7)*	70.9±19.2; −21.5 (−30.7-−18.0)*
RE			
18-40	67.7±39.4	54.4±43.3; −13.4 (−24.2-5.5) (NS)	82.5±25.7; 14.7 (2.1-22.8)*
41-60	75.0±37.0	22.6±30.0; −52.4 (−74.6-−36.4)*	47.2±48.1; −27.2 (−49.0-−6.5)*
MH			
18-40	71.8±15.6	63.6±13.9; −8.7 (−14.8-−2.6)*	67.8±12.8; −4.0 (−11.1-3.0) (NS)
41-60	73.1±17.6	61.0±20.1; −12.1 (−20.6-−1.8)*	68.3±19.0; −4.7 (−12.8-6.3) (NS)

*Significant at *P*<0.01. Normal range: Based on the study by Lam *et al*.[14] NS=Not significant, PF=Physical functioning, RP=Role physical, BP=Body pain, GH=General health, VT=Vitality, SF=Social functioning, RE=Role emotional, MH=Mental health, SF-36=Short form-36, CI=Confidence interval, SD=Standard deviation

Table 8: Health-related quality of life (short form-36) among coronavirus disease 2019 survivors (*n*=60) who did not require intensive care unit admission at 3, and 6 months after illness onset in comparison with normative data stratified into different age groups

SF-36 domains/ age group (years)	Normal, mean±SD	3 months versus normal, mean±SD; mean (95% CI)	6 months versus normal, mean±SD; mean (95% CI)
PF			
18-40	96.3±6.6	82.8±15.8; −13.5 (−16.0-−7.0)*	88.1±16.5; −8.2 (−13.4-−5.2)*
41-60	90.6±12.4	59.5±24.6; −31.1 (−42.2-−15.8)*	64.1±25.6; −26.6 (−40.2-−12.9)*
RP			
18-40	85.6±27.7	59.7±41.8; −25.9 (−45.7-−20.4)*	70.0±40.7; −15.6 (−20.1-0.1)*
41-60	81.6±31.7	38.1±32.8; −43.5 (69.3-−35.7)*	28.1±41.7; −53.5 (−75.9-−37.6)*
BP			
18-40	86.4±19.4	70.2±22.2; −16.2 (−22.5-−2.1)*	76.9±25.8; −9.5 (−20.6-−8.9)*
41-60	82.6±22.9	42.9±18.7; −39.7 (−51.0-−28.3)*	47.7±24.9; −34.9 (−48.2-15.2)*
GH			
18-40	59.5±19.4	58.2 (14.4); −1.3 (−6.1-2.9) (NS)	58.4±18.8; −1.1 (−8.6-2.1) (NS)
41-60	53.2±20.1	40.3 (11.6); −13.0 (−17.6-−5.3)*	36.3±16.5; −16.9 (−23.3-−7.1)*
VT			
18-40	60.2±18.3	45.8±11.2; −14.4 (−18-−6.8)*	49.5±11.2; −10.7 (−16.0-−9.4)*
41-60	60.3±18.9	39.7±9.6; −20.6 (−35.5-−15.2)*	38.1±15.5; −22.2 (−35.5-−14.9)*
SF			
18-40	90.2±16.2	74.0±11.9; −16.2 (−24.5-−10.3)*	75.0±12.8; −15.3 (−26.4-−8.6)*
41-60	92.4±16.5	53.9±25.7; −38.5 (−55.8-−26.8)*	59.4±29.8; −33.0 (−49.0-−17.4)*
RE			
18-40	67.7±39.4	66.0±41.8; −1.7 (−12.9-5.4) (NS)	76.0±34.4; 8.3 (−2.8-0.207) (NS)
41-60	75.0±37.0	32.7±38.9; −42.3 (−65.9-−20.0)*	46.8±46.7; −28.2 (−46.1-−13.7)*
MH			
18-40	71.8±15.6	69.6±16.9; −2.2 (−8.9-3.2) (NS)	67.0±15.1; −4.8 (−8.7-−1.2)*
41-60	73.1±17.6	50.8±16.3; −22.3 (−30.0-−12.0)*	55.0±16.7; −18.1 (−25.6-−10.2)*

*Significant at *P*<0.05. Normal range: Based on the study by Lam *et al*.[14] NS=Not significant, PF=Physical functioning, RP=Role physical, BP=Body pain, GH=General health, VT=Vitality, SF=Social functioning, RE=Role emotional, MH=Mental health, SF-36=Short form-36, CI=Confidence interval, SD=Standard deviation

patients who were treated on medical wards, suggesting severe lung injury.

6MWD was performed to evaluate the global and integrated responses to exercise. Although showing considerable improvement over 6 months follow-up, the 6MWD was substantially reduced for all age groups at 3 and 6 months when compared with normal control of the same age groups.

Although the relatively well-preserved lung function in most of our COVID-19 survivors, the poor performance in the 6MWT was noted in most age groups. This could be attributed to muscle wasting and myopathy. The long period of bed rest and hospitalization could lead to muscle wasting and physical deconditioning. In addition to using systemic corticosteroid therapy could contribute to myopathy.[24,25]

Table 9: Correlations among health-related quality of life, pulmonary function, and 6 min walk distance at 6 months (*n*=85)

SF-36 domains	FVC	FEV_1	VC	TLC	DLCO	6MWD
PF	0.01*	0.01*	0.01*	0.13	0.32*	0.02*
RP	0.02*	0.27*	0.04*	0.06	0.22*	0.37*
BP	0.13	0.09	0.19	0.04	0.09	0.27*
GH	0.41*	0.02*	0.41*	0.01*	0.11*	0.03*
VT	0.21*	0.16	0.23*	0.07	0.16	0.02*
SF	0.21*	0.24*	0.05*	0.03	0.21*	0.30*
RE	0.02*	0.21*	0.02*	0.09	0.01*	0.01*
MH	0.15	0.01*	0.16	0.06	0.12	0.08*

*Significant at $P<0.05$. Values shown are Pearson's correlation coefficients (r). PF=Physical functioning, RP=Role physical, BP=Body pain, GH=General health, VT=Vitality, SF=Social functioning, RE=Role emotional, MH=Mental health, SF-36=Short form-36, FVC=Forced vital capacity, FEV_1=Forced expiratory volume in 1 s, TLC=Total lung capacity, VC=Vital capacity, DLCO=Diffusing capacity for carbon monoxide, 6MWD=Six minute walking distance

After controlling age and gender, our analysis has shown that the total CT severity score and DLCO% predicted were positive independent predictors associated with lower 6MWD at 6 months.

A paucity of studies who assessed health status in COVID-19 survivors. The present study showed a significant impairment of health status in most SF-36 domains among our patients at 6 months. Furthermore, significant positive correlations between SF-36 domains and lung function indices (VC, FVC, FEV1, and DlCO) and 6MWD. The results are not surprising as, the physical impairment, the long period of isolation and extreme uncertainty during the COVID-19 pandemic causes panic and mental health problems for the general population. This can influence the general health and quality of life of people.[26,27]

Conclusion

The exercise capacity and health status of COVID-19 survivors was considerably lower than that of a normal population at 6 months. Significant alterations in lung function, with a mainly impaired DLCO persisting at 6 months after recovery was noted in 29.4% of survivors. Thus, Further, follow-up is needed to assess if these deficits are persistent. Performing comprehensive assessment and rehabilitation programs should be performed for the detection and management of any persistent or emerging long-term sequelae in the radiological and physiological domains. The strengths of this study are the serial PFT and 6MWD assessment in COVID 19 patients at 3 and 6 months duration, and the CT assessment of the extent of lung involvement during the acute phase.

Limitations

First, the lack of baseline pulmonary function test results before illness; making it difficult to make a comparison with the results after the illness. There were only a minority of patients with chronic respiratory disease, so it should be acceptable to speculate that the basic lung function interpretation in the majority of patients would be normal.

Second, we did not perform chest CT at 3 and 6 months, due to limited access. The association between CT images and the lung function parameters was not analyzed in our study. Finally, due to the absence of approved specific treatment, we could not assess the effect of treatment on functional recovery.

Longer follow-up on COVID-19 patients should be made to observe the characters and change the tendency of lung function and exercise tolerance.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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