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Midterm follow-up of healthy young adults with moderate to severe COVID-19: pulmonary and extrapulmonary disease sequelae

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Abstract

Background Follow-up studies on coronavirus disease 2019(COVID-19) were mainly focused on short-term sequelae in patients with comorbid diseases. The aim of this study was to investigate the pulmonary and extrapulmonary sequelae of moderate to severe COVID-19 in the midterm follow-up of healthy young adults.

Methods In this prospective cohort study, we used the hospital information system (HIS) to identify patients who had recovered from moderate to severe COVID-19 without comorbidity. All eligible patients were invited to participate in the study. Participants were asked to fill out a set of questionnaires to evaluate fatigue, anxiety, and post-traumatic stress disorder (PTSD). They also underwent chest computed tomography (CT) scan, pulmonary function test (PFT), and tissue doppler imaging (TDI) echocardiography. A blood sample and a 12-lead electrocardiogram (ECG) were obtained.

Results A total of 50 recovered patients and 12 healthy controls were enrolled in the study. Fifteen out of 50 patients received intensive care. Patients had significantly higher fatigue and anxiety scores than controls. PTSD criteria were met in 29 out of 50 patients. Ground glass opacities, nodules, and subpleural lines were the most frequent abnormalities in chest CT scans of patients. Patients had significantly lower left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) than controls (*P* value 0.019 and < 0.001, respectively).

Conclusions According to our findings, COVID-19 survivors might experience anxiety, fatigue, PTSD, pulmonary impairment, leading to reduced cardiac function up to 6 months after discharge.

Keywords COVID-19, Follow-up, Sequelae, Tissue doppler imaging echocardiography, Lung CT scan

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Introduction

During the ongoing pandemic, approximately 269 million people have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), of whom 243 million have recovered as of 13th December 2021 [1]. Hundreds of thousands of people are getting infected with COVID-19 every day, and a significant proportion of them recover from the disease.

A good deal of literature has focused on the treatment and course of the illness and vaccination against it. As the number of the recovered COVID-19 patients increases, there is a concern about the post-acute and long-term sequelae, also known as long COVID [2]. According to previous literature, the severity of COVID-19 is associated with that of sequelae [3].

The radiological findings on the lung computed tomography (CT) scan, laboratory and pulmonary function test findings, mental health disturbances, and cardiac workup in the short-term follow-up have been studied [2, 4–8]. Most studies included old patients with comorbidities [9].

An increasing number of studies have investigated mid-to-long-term sequelae of COVID-19 in the young population. According to a recent systematic review, long-term follow-up in healthy young adults, especially cardiac and pulmonary sequelae of COVID-19, has yet to be studied [9]. Therefore, this study aimed to investigate the pulmonary and extrapulmonary sequelae of moderate to severe COVID-19 in the midterm follow-up of healthy young adults.

Materials and methods

Study design

We conducted a prospective cohort study on moderate to severe COVID-19 survivors to investigate the pulmonary and extrapulmonary midterm sequelae.

The study population

The study population in the exposed group consisted of COVID-19 survivors aged 18–50 without underlying medical conditions who were hospitalized in Hospitals affiliated to Alborz University of Medical Sciences in Karaj, Iran, between April 3, 2020, and August 22, 2020. We identified them using a hospital information system (HIS).

The unexposed participants were recruited from healthy hospital staff younger than 50 years without a history of COVID-19.

The study inclusion criteria for recruiting COVID-19 Survivors were as follows:

- Having a positive real-time reverse transcriptase polymerase-chain-reaction (RT-PCR) test result for SARS-CoV-2
- Aged 18 to 50 years
- Having a minimum of 1 month from the discharge date
- Without underlying medical conditions (including diabetes mellitus, hypertension, hypo/hyper-thyroidism, cardiovascular disease, autoimmune disease, pulmonary disease, hepatic dysfunction, kidney dysfunction)

Exclusion criteria

- Unwillingness to participate in the study

Ethical approval statement

The ethics committee of Alborz University of Medical Sciences approved the study protocol . The written informed consent was obtained from all the participants.

Data collection

The patients' medical records were reviewed to collect the demographics and clinical characteristics, and contact information of the participants . All patients were contacted by phone to invite them to participate in the study. Participants were asked to fill out a series of questionnaires, including the brief fatigue inventory (BFI), post-traumatic stress disorder checklist (PCL), Hamilton, 36-item short-form survey (SF-36), and the demographic data questionnaire. On the follow-up visit, patients underwent a chest CT scan, PFT, TDI echocardiography, and also a blood sample, and a standard 12-lead electrocardiography were obtained. The participants' weight and height were also measured and recorded.

Questionnaires

The first questionnaire consisted of demographic data, filled out by the participants, and heart rate and blood pressure were measured by a team member. The brief fatigue inventory (BFI) was used to measure fatigue intensity and its interference with daily activity. BFI is composed of nine to eleven-point (0 to 10) scale. A mean BFI score was calculated. A mean BFI score greater than or equal to seven is considered severe fatigue [10].

The post-traumatic stress disorder checklist for civilians (PCL-C) is a 17-item questionnaire measuring 17 Diagnostic and statistical manual of mental disorders (DSM-IV) symptoms ranging from 1 to 5. A total score greater than 33 is considered diagnostic for

post-traumatic stress disorder (PTSD) [11]. Hamilton anxiety scale (HAMA) is a questionnaire consisting of 14- to 5-point scale [12].

The 36-item short-form survey (SF-36) was used to measure eight health concepts as follows: physical functioning (10 items), role limitations due to physical health (4 items), role limitations due to mental health (3 items), energy (4 items), emotional well-being (5 items), social functioning (2 items), pain (2 items), and general health (5 items) [13].

Pulmonary function test and chest computed tomography (CT) scan

A technician performed pulmonary function tests. The pulmonary function included forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FFVC, forced mid-expiratory flow (FEF25-75%), and peak expiratory flow (PEF). Parameters were reported as a percentage (%) of the reference value for each patient, calculated by Global Lung Function 2012 equations [14].

CT scan images were acquired with the patient in the supine position at the end of inhalation using a 64-row CT scanner. Two senior cardiothoracic radiologists reviewed all CT images in random order who were not aware of any clinical or laboratory findings or patient outcomes. The readers independently assessed the CT features using axial and multiplanar reconstructed images. After the independent evaluation, the radiologists resolved any disagreement with discussion and consensus.

Tissue doppler echocardiography

Echocardiographic examinations were performed in the left lateral decubitus position. An ultrasound instrument (affinity 70, Phillips medical system) was used with an S5 transducer. All the measurements were performed by a single experienced echocardiography fellow in order to avoid inter-observer variability.

Lab data

Blood samples were taken for the measurement of lipid, glucose, iron, and coagulation profiles, liver enzymes, kidney and thyroid function tests, serum vitamin D3, electrolytes, uric acid, albumin, magnesium, and creatine kinase myocardial band (CPK-MB), and SARS-CoV-2 IgM and IgG level, quantitative troponin I, and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and complete blood count (CBC) with differentials.

Statistical analysis

Variables were summarized using median (interquartile range (IQR)) or percentage (number), as appropriate. Mann-Whitney test, chi-square test, and Fisher's exact analysis were used to compare the study groups. A significance level of 0.05 was used in all analyses. Statistical analyses were performed using SPSS Version 21.0.

Results

A total of 50 COVID-19 survivors with moderate to severe disease (response rate 10%) and 12 healthy controls provided their written informed consent to participate in our study. There were no significant differences between the two groups with respect to age and gender, but compared to controls, COVID-19 patients had a higher body mass index (BMI) (28.1 (26.1–30.2) vs. 24.8 (23.7–28.0)) and were less educated (college level 32% vs. 75%).

In the COVID-19 group, the median length of hospital stay was seven days (interquartile range ((IQR) 5 to 10); 15 patients received intensive care during the hospitalization, of whom three underwent invasive mechanical ventilation. The median time from discharge to follow-up was 6 months (IQR 3 to 7 months) (Table 1).

Laboratory findings at the follow–up time are presented in Table 2. A lower concentration of AST (median (IQR) 26.0 (20.8–32.0) vs. 35.0 (30.5–39.0) U/L), albumin (4.5 (3.9–4.7) vs. 4.9 (4.7–5.1) g/L), direct bilirubin (0.19 (0.1–0.2) vs. 0.2 (0.2–0.4) mmol/L), HDL (44.5 (39.7–54.0) vs. 62 (51–67) mg/Dl), LDL (112 (97–137) vs. 140 (114–157) mg/dL), and TSH (1.65 (0.78–2.43) vs. 2.05 (1.8–3.2) mIU/L) was found in COVID-19 survivors compared to controls, but a higher level of FBS (94.5 (86.8–100.0) vs. 81.0 (75.3–99.0) mmol/L), HbA1C (5.05 (4.7–5.43) vs. 4.6 (4.2–5.0) %), and mg (2.4 (2.1–2.5) vs. 2.1 (1.95–2.20) mg/Dl) was observed in COVID-19 survivors compared to controls. (all P value < 0.05).

Compared to other patients, COVID-19 patients admitted to the ICU had a higher level of Ferritin (136.0 (93.0–219.0) vs. 59.0 (14.0–104.0) ng/ml), total bilirubin (0.7 (0.4–1.2) vs. 0.5 (0.4–0.7) mmol/L), LDH (348 (299–391) vs. 282 (256–341) U/L), and D3 (23.0 (20.0–33.0) vs. 18.0 (12.0–23.0) ng/ml), (all P value < 0.05) but had a lower concentration of Albumin (4.0 (3.8–4.6) vs. 4.5 (4.0–4.8) g/L; P value = 0.052).

In addition, COVID-19 patients admitted to the ICU had a higher serum IgG level than other patients (7.8 (2.2–10.5) vs. 1.7 (1.2–3.3) g/L; P value = 0.017).

Health-related quality of life (HRQoL) and mental health

COVID-19 survivors had a lower score in all SF-36 dimensions compared to controls; however, these differences were not statistically significant in two domains: emotional well-being and social functioning (Table 3) (both P value > 0.05).

Symptom score for anxiety in COVID-19 patients was higher than that in controls (HAM-A median score (IQR)

Table 1 Characteristics of the participants by study group

Variables	Case *N* = 50	Control *N* = 12	*P* value
Age (year), median (IQR)	39 (36, 46)	37 (30, 42)	0.106
Male gender, % (*N*)	64% (32)	75% (9)	0.470
BMI, median (IQR)	28.1 (26.1, 30.2)	24.8 (23.7, 28.0)	**0.045**
Education % (*N*)			
College	32% (16)	75% (9)	0.018
High school	42% (21)	17% (2)	
Middle school	26% (13)	3% (1)	
Symptoms at admission % (*N*)			
Fever	44% (22)	–	–
Cough	68% (34)	–	–
Tiredness	20% (10)	–	–
Shortness of breath	42% (21)	–	–
Spo2 < 93%	40% (20)	–	–
Chest involvement	96% (48)	–	–
Gastrointestinal symptoms	4% (2)	–	–
CNS/PNS symptoms	0.0% (0)	–	–
Chest pain	0.0% (0)	–	–
Hospital care			
Received ICU care	33% (15)	–	–
Invasive mechanical ventilation	6% (3)	–	–
Length of hospital stay (day), median (IQR)	7 (5, 10)	–	–
Time from discharge to follow-up (month), median (IQR)	6 (3, 7)	–	–

BMI body mass index, *CNS* central nervous system, *ICU* intensive care unit, *IQR* inter quartile range, *PNS* peripheral nervous system, *Spo2* pulse oximeter saturation
All boldface entries are significant in this version

13.0 (7.5, 20.5) vs. 4.0 (2.3, 7.8), *P* value < 0.001). However, symptoms of moderate to severe anxiety [a HAM-A score of 25 to 30] were observed in 20 % of COVID-19 patients and none of the controls.

Twenty-nine out of 50 COVID-19 patients met positive criteria for PTSD symptoms according to the PCL-C score [PCL ≥ 33].

Patients significantly had higher fatigue scores than controls (BFI median score (IQR) 4.78 (2.72, 6.56) vs. 2.67 (1.89, 3.11), *P* value = 0.004); 7 participants in COVID-19 group (14%) and no participant in control group had severe fatigue (BFI score 7 to 10).

No statistically significant differences were found between ICU and non-ICU patients in terms of HRQoL, fatigue, and anxiety levels, but non-ICU patients more frequently reported symptoms of PTSD than ICU patients (71% (25) vs. 27% (4), *P* value = 0.004).

Pulmonary function and chest computed tomography (CT) scan findings

A total of 47 COVID-19 survivors received the lung function test. Abnormalities in FVC, FEV1, and FEV1/FVC % predicted were observed in 6/47 (12.8%), 14/47 (29.8%), and 5/47 (11%), respectively. Proportion of patients with FEF 25-75 and peak expiratory flow % predicted < 80 were 55% (26) and 68% (32), respectively (Table 4).

During the hospitalization, 45 out of 50 COVID-19 patients had abnormalities on chest CT scans.

On follow-up CT imaging of these patients, 57.8% (26) of patients had consolidation was found in one of them. Subpleural line, Nodules, and radiological signs of fibrosis were present in 11.1% (5), 22.2% (10), and 33.3% (15) of patients, respectively. No patient had reticulation. Left and right S1 ($N = 6$), S2 ($N = 6$), and S3 ($N = 7$) were the most frequently involved segments (Table 4).

No significant differences were detected between ICU and non-ICU admitted patients with respect to the evaluated spirometry and CT scan parameters.

Cardiac evaluation

High-sensitivity troponin T concentration was within the normal range in all participants.

On standard ECG, 86% (43) of COVID-19 patients had normal sinus rhythm. In other patients, ECG rhythm findings include sinus bradycardia ($n = 3$), left anterior fascicular block ($n = 2$), and right bundle branch block

Table 2 Laboratory findings at follow-up time of the study population

Variables	Case			Control *N* = 12	PV_1	PV_2
	All, *n* = 50	Non ICU, *n* = 35	ICU, *n* = 15			
WBC count, × 10^9/L	6.6 (5.5–7.4)	6.7 (5.7–7.5)	6.5 (5.0–7.1)	6.0 (5.4–7.1)	0.382	0.656
RBC, × 10^9/L	5.2 (4.7–5.4)	5.1 (4.7–5.4)	5.3 (4.8–5.5)	5.2 (4.8–5.5)	0.599	0.262
Ferritin, ng/ml,	91.0 (34.0–148.5)	59.0 (14.0–104.0)	136.0 (93.0–219.0)	47.0 (18.7–190.0)	0.460	**0.002**
Platelet count, × 10^3/Ml	224 (195–260)	226 (200–269)	221 (186–247)	201 (189–245)	0.226	0.433
Hematocrit, %	43.8 (39.4–45.8)	43.9 (38.6–45.9)	43.7 (40.7–45.1)	44.8 (41.9–47.4)	0.162	0.791
Hb, g/dL	15.0 (13.3–15.8)	14.9 (13.3–15.7)	15.1 (13.8–15.8)	15.7 (14.2–16.7)	0.059	0.641
AST, U/L	26.0 (20.8–32.0)	26.0 (20.0–32.0)	27.0 (22.0–34.0)	35.0 (30.5–39.0)	**0.009**	0.491
ALT, U/L	28.0 (18.0–41.8)	28.0 (18.0–40.0)	29.0 (18–50)	31.0 (24.3–42.3)	0.580	0.816
ALP	163.5(138–202)	163 (136–199)	180 (150–207)	161 (140–171)	0.605	0.849
Albumin, g/L	4.5 (3.9–4.7)	4.5 (4.0–4.8)	4.0 (3.8–4.6)	4.9 (4.7–5.1)	**0.004**	**0.052**
Total bilirubin, mmol/L	0.5 (0.4–0.8)	0.5 (0.4–0.7)	0.7 (0.4–1.2)	0.3 (0.3–0.6)	0.078	**0.035**
Direct bilirubin, mmol/L	0.19 (0.1–0.2)	0.2 (0.1–0.2)	0.2 (0.20.2)	0.2 (0.2–0.4)	**0.018**	0.705
Uric acid, mg/dl	4.4 (3.3–5.2)	4.1 (2.9–5.2)	4.4 (4.0–5.9)	3.9 (3.2–5.2)	0.910	0.127
BUN, mmol/L	26.0 (20.0–31.0)	25.0 (20.0–31.0)	28.0 (20.0–36.0)	23.0 (21.0–29.0)	0.319	0.539
Creatinine, mg/dl	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.1 (0.9–1.2)	1.1 (0.9–1.3)	0.386	0.780
FBS, mmol/L	94.5 (86.8–100.0)	96.0 (87.0–100.0)	91.0 (86.0–101.0)	81.0 (75.3–99)	**0.015**	0.890
HbA1C, %	5.05 (4.7–5.43)	5.0 (4.8–5.4)	5.2 (4.6–5.5)	4.6 (4.2–5.0)	**0.004**	0.983
TG, mmol/L	103 (82–158)	102 (80–153)	148 (83–192)	131 (83–168)	0.768	0.421
HDL, mg/dL	44.5 (39.7–54.0)	44 (39–58)	48 (42–50)	62 (51–67)	**0.004**	0.807
LDL, mg/dL	112 (97–137)	110 (96–127)	114 (99–140)	140 (114–157)	**0.012**	0.465
Cholesterol	173.5 (153.8–– 200.3)	168 (146–200)	175 (157–211)	177 (157–192)	0.760	0.357
PT ratio	1.0 (1.0–1.04)	1.0 (1.0–1.04)	1.0 (1.0–1.0)	1.04 (1.00–1.08)	0.086	0.379
INR	1.0 (1.0–1.05)	1.0 (1.0–1.05)	1.0 (1.0–1.0)	1.05 (1.00–1.10)	0.090	0.401
PTT	30.0 (29.0–31.0)	31.0 (29.0–31.0)	30.0 (29.0–32.0)	30.0 (29.5–31.8)	1.00	0.817
ESR 1st, mm/h	5.0 (2.0–14.0)	5.0 (3.0–14.0)	4.0 (2.0–16.0)	5.0 (2.0–9.0)	0.692	0.693
LDH, U/L	301 (259–353)	282 (256–341)	348 (299–391)	278 (264–315)	0.285	**0.015**
CPK-MB, U/L	18.5 (14.0–24.0)	18.0 (13.0–24.0)	20.0 (17.0–24.0)	15.0 (14.7–16)	0.073	0.156
Q-CRP, mg/L, 10 ≤	2.0 (1.37–2.3)	1.5 (1.2–2.1)	2.0 (1.4–3.0)	1.9 (1.5–2.7)	0.650	0.369
Troponin I, ng/ml < 0.04	0.12 (0.10–0.20)	0.14 (0.11–0.18)	0.1 (0.05–0.2)	0.12 (0.12–0.16)	0.789	0.293
TSHn, mIU/L	1.65 (0.78–2.43)	1.7 (0.7–2.4)	1.3 (0.8–3.6)	2.05 (1.8–3.2)	**0.041**	0.751
D3, ng/ml	19.5 (15.0–25.0)	18.0 (12.0–23.0)	23.0 (20.0–33.0)	21.5 (14.3–30.8)	0.544	**0.015**
Mg, mg/dL	2.4 (2.1–2.5)	2.4 (2.1–2.5)	2.2 (2.0–2.6)	2.1 (1.95–2.20)	**0.016**	0.481
SARS-Cov2-IgM, U/mL	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	–	–	0.757
SARS-Cov2-IgG, U/mL	2.2 (1.35–8.7)	1.7 (1.2–3.3)	7.8 (2.2–10.5)	–	–	**0.017**

(PT.patient-PT.control)/PT.control

PT ratio (*patient time* divided by mean normal *PT*)

AST aspartate transaminase, *ALT* alanine transaminases, *BUN* blood urea nitrogen, *Hb* hemoglobin. *LDH* lactate dehydrogenase, *ESR* erythrocyte sedimentation rate, *Q-CRP* quick-read C-reactive protein, *CPK-MB* creatine kinase myocardial band, *ICU* intensive care unit, *INR* international normalized ratio, *IQR* interquartile range, *PT* prothrombin time, *WBC* white blood cell

troponin I levels: Normal range: below 0.04 ng/ml. Probable heart attack: above 0.40 ng/ml

Feritenine

20 to 250 ng/mL for adult males

10 to 120 ng/mL for adult females, 18 to 39 years

12 to 263 ng/mL for females, 40 years and older

($n = 2$). The most common ECG changes, in order by frequency, were ST elevation ($n = 18$), Tall R wave ($n = 17$), inverted T wave ($n = 16$), and biphasic T wave ($n = 15$) (Table 5).

On echocardiography, COVID-19 group compared to controls had significantly lower LV end diastolic echo dimensions (LVEDD) (median (IQR) 4.33 (4.00, 4.55) vs. 4.53 (4.40, 4.80); P value = 0.019) and left ventricular end

Table 3 Health-related quality of life (HRQoL) and mental health

Variables	Case			Control *N* = 12	PV1	PV 2
	All Median (IQR)/% (*N*)	Non-ICU Median (IQR)/% (*N*)	ICU Median (IQR)/% (*N*)			
Weight change, %	−0.5 (−5.6, +0.29)	0.0 (−4.8, +1.5)	−2.6 (−9.5, 0.0)	–	–	0.317
SF-36 domains						
Physical functioning	75.0 (60.0, 90.0)	75.0 (57.5, 90.0)	75.0 (60, 90)	87.5 (78.7, 96.3)	**0.028**	0.532
Role limitations due to physical health	87.5 (25.0, 100)	75.0 (25.0, 100)	100 (0.0, 100)	100 (100, 100)	**0.013**	0.706
Role limitations due to emotional health	66.7 (0.0, 100)	33.0 (0.0, 100)	100 (33.0, 100)	100 (66.7, 100)	**0.013**	0.063
Energy	55.0 (36.3, 65.0)	50.0 (37.5, 65.0)	60.0 (35.0, 70.0)	62.5 (60.0, 75.0)	**0.018**	0.385
Emotional well-being	60.0 (45.0, 76.0)	56.0 (42.0, 68.0)	72.0 (52.0, 80.0)	68.0 (61.5, 72.0)	0.185	0.118
Social functioning	62.5 (37.5, 75.0)	50.0 (37.5, 75.0)	62.5 (50.0, 87.5)	75.0 (59.4, 87.5)	0.051	0.177
Pain	67.5 (55.6, 77.5)	67.5 (50.0, 77.5)	67.5 (57.5, 87.5)	90.0 (75.0, 100)	**0.002**	0.589
General health	55.0 (35.0, 73.8)	55.0 (35.0, 70.0)	60.0 (45.0, 80.0)	70.0 (65.0, 80.0)	**0.014**	0.429
Brief Fatigue Inventory (BFI)	4.78 (2.72, 6.56)	5.11 (2.89, 6.56)	3.78 (2.11, 6.22)	2.67 (1.89, 3.11)	**0.004**	0.258
BFI score ≥ 7	14.0% (7)	20.0%(7)	0.0% (0)	0.0% (0)	0.328	0.087
Hamilton Anxiety Scale (HAM-A)	13.0 (7.5, 20.5)	13.0 (9.0, 22.0)	11.0 (6.0, 17.0)	4.0 (2.3, 7.8)	**< 0.001**	0.386
HAM-A score 25 to 30	20% (10)	20% (7)	20% (3)	0.0% (0)	0.188	1.00
Post-traumatic stress disorder Checklist (PCL)	39.0 (28.0, 51.3)	44.0 (29.0, 52.0)	29.0 (20.0, 45.0)	–	–	**0.039**
PCL score > 33	58.0%(29)	71.4% (25)	27% (4)	–	–	**0.004**

All boldface entries are significant in this version

Table 4 CT-scan and pulmonary function test findings

Parameters	All Cases Median (IQR)/% (*N*)	Non-ICU Median (IQR)/% (*N*)	ICU Median (IQR) /% (*N*)	*P* value
Spirometry				
FVC, % predicted	110 (90, 125)	109 (89, 121)	122 (95, 125)	0.295
< 80%	12.8% (6)	12.5% (4)	13.3% (2)	1.00
FEV1, % predicted	91 (75, 109)	88.5 (76.0, 101.3)	93.0 (70.0, 120.0)	0.487
< 80%	29.8% (14)	31.3% (10)	26.7% (4)	1.00
FEV1/FVC, % predicted	96 (79, 109/)	97 (78, 103)	94 (81, 102)	0.879
< 70%	11% (5)	13% (4)	7% (1)	0.660
FEF 25–75, % predicted	70.0 (52.0, 89.0)	69.5 (53.3, 86.3)	77.0 (35.0, 94.0)	0.977
< 80%	68% (32)	72% (23)	60% (9)	0.416
Peak expiratory flow, % predicted	75.0 (49.0, 100)	72.5 (47.5, 96.0)	82.0 (51.0, 115.0)	0.356
< 80%	55% (26)	59% (19)	47% (7)	0.533
Computed tomography (CT)				
Ground-glass opacity	57.8% (26)	50.0% (15)	73.3% (11)	0.135
Consolidation	2.2% (1)	0.0% (0)	6.7% (1)	0.333
Fibrosis	33.3% (15)	30.0% (9)	40.0% (6)	0.502
Subpleural line	11.1% (5)	6.7% (2)	20.0% (3)	0.315
Reticulation	0.0% (0)	0.0% (0)	0.0% (0)	–
Nodules	22.2% (10)	26.7% (8)	13.3% (2)	0.310

systolic diameter (LVESD) (2.1 (2.1, 2.3) vs. 2.4 (2.4, 2.8)), and Septal-Em (7.9 (6.2, 9.4) vs. 9.4 (8.0, 11.2), *P* value = 0.049) values (Table 5).

Left ventricle ejection fraction (LVEF) less than 50% was observed in three COVID-19 patients, and the ICU-admitted patient group, but none of the controls. In addition, Global longitudinal strain (GLS) less than 16% was more frequently detected in COVID-19 patients (20% (9)) than controls (9% (1), bur their difference were not statistically significant.

Table 5 Echocardiographic and electrocardiographic findings

Cases, median (IQR)/% (*N*)			Control Median (IQR)/% (*N*)	PV1	PV 2
All	**Non-ICU**	**ICU**			
110 (110, 120)	110 (105, 120)	110 (110, 126)	115 (102, 120)	0.978	0.647
70 (70, 80)	70 (70, 80)	70 (67, 70)	75 (62, 93)	0.579	0.349
78 (70 – 81)	76 (68, 80)	80 (76, 82)	84 (79, 91)	**0.029**	**0.035**
Electrocardiographic measures					
ECG rhythm					
86%(43)	83% (29)	93% (14)	–	–	1.000
6% (3)	6% (2)	7% (1)	–		
4% (2)	6% (2)	0% (0)	–		
4% (2)	6% (2)	0% (0)	–		
14% (7)	11% (4)	20% (3)	–	–	0.415
8% (4)	9% (3)	7% (1)	–	–	1.000
34% (17)	34% (12)	33% (5)	–	–	0.948
36% (18)	40% (14)	27% (4)	–	–	0.368
32% (16)	29% (10)	40% (6)	–	–	0.427
30% (15)	37% (13)	13% (2)	–	–	0.092
20% (10)	20% (7)	20% (3)	–	–	1.000
8% (4)	9% (3)	7% (1)	–	–	1.000
28% (14)	29% (0)	27% (4)	–	–	0.891
407 (385, 424)	402 (351, 426)	413 (392, 423)	–	–	0.396
8% (4)	6% (2)	13% (2)	–	–	0.574
Echocardiography					
6% (3)	0% (0)	21% (3)	0% (0)	1.000	**0.022**
30% (14)	18% (6)	57% (7)	17% (2)	0.482	**0.008**
4.33 (4.00, 4.55)	4.36 (4.00, 4.56)	4.17 (3.74, 4.61)	4.53 (4.40, 4.80)	**0.019**	0.496
2.1 (2.1, 2.3)	2.1 (2.1, 2.25)	2.1 (1.8, 2.4)	2.4 (2.4, 2.8)	**< 0.001**	0.563
− 18.2 (− 19.6, − 17.1)	− 18.7 (− 20.4, − 17.3)	− 17.3 (− 18.9, − 14.8)	− 19.0 (− 19.6, − 18.0)	0.347	**0.026**
46% (21)	38% (12)	64% (9)	27% (3)	0.267	0.093
20% (9)	9% (3)	43% (6)	9% (1)	0.412	**0.015**
7.9 (6.2, 9.4)	8.0 (7.0, 9.8)	6.0 (4.8, 9.1)	9.4 (8.0, 11.2)	**0.049**	**0.026**
12.0 (9.8, 14.0)	12.5 (10.2, 14.5)	11.3 (7.8, 13.3)s	12.0 (10.5, 15.0)	0.820	0.098
2.92 (2.80, 3.20)	2.80 (2.80, 3.10)	3.13 (2,85, 3.27)	2.77 (2.68, 2.98)	0.062	0.077
10.0 (9.0, 11.8)	10.0 (9.1, 11.2)	10.2 (8.5, 12.1)	10.0 (9.3, 11.6)	0.878	0.930
0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	–	–
21.0 (19.0, 23.0)	21.0 (20.0, 22.8)	20.0 (18.0, 23.5)	22.5 (21.0, 24.0)	0.081	0.454
24% (11)	19% (6)	39% (5)	10% (1)	0.317	0.163
− 18.6 (− 21.8, − 14.9)	− 19.1 (− 22.0, − 15.1)	− 17.4 (− 21.1, − 11.5)	− 20.0 (− 22.6, − 16.0)	0.117	0.093
20.0 (20.0, 22.3)	20.0 (20.0, 23.0)	20.0 (20.0, 22.0)	21.0 (21.0, 22.5)	0.124	0.400
2% (1)	3% (1)	0.0% (0)s	0.0% (0)	1.00	1.00
0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	–	–

Values are in median and interquartile range, or *n* (%) E/e' early mitral inflow velocity/mitral annular early diastolic velocity, *EF* ejection fraction, *IQR* interquartile range, *LV* left ventricular, *LVEDd* left ventricular end-diastolic dimension, *LVESd* left ventricular end-systolic dimension, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *RV* right ventricular, *RV S'* right ventricular systolic excursion velocity, *TAPSE* tricuspid annular plane systolic excursion

RVLS right ventricular longitudinal strain, *PASP* pulmonary artery systolic pressure, *TR* tricuspid regurgitation

Visually estimated impaired right ventricular function, *n* (%)

QTc is prolonged if > 440 ms in men or > 460 ms in women

All boldface entries are significant in this version

A higher proportion of ICU-admitted patients had abnormal LV diastolic dysfunction than non-ICU patients.

Discussion

In this study, we presented follow-up data of patients with moderate to severe COVID-19, 6 months after discharge from the hospital. One-fifth of patients had moderate to severe anxiety, more than half met PTSD criteria, and seven reported extreme fatigue. More than half of the patients had GGO without consolidation on chest CT imaging. GGO, nodule, and subpleural lines were the most frequent abnormalities in chest CT. In this study, the rate of restrictive lung impairment was approximately 12% after 6 months of discharge. More than half of the survivors had impaired peak expiratory flow rate or FEF 35–75. Patients had significantly lower LVEDD, LVESD, and septal-Em than the control group. Serum SARS-CoV-2 IgG concentration was higher in ICU admitted patients. Non-ICU patients reported PTSD symptoms more frequently compared to ICU-admitted patients. Pulmonary function tests and chest CT scans findings were similar between ICU and non-ICU admitted patients. Three ICU admitted patients had a LVEF less than 50%.

Our findings are in line with previous studies reporting that a large number of COVID-19 survivors would suffer from fatigue, anxiety, PTSD, and reduced quality of life weeks after the infection was subsided. These psychiatric disorders were reported up to 3 years after SARS-CoV and Middle East respiratory syndrome (MERS) infections [9]. ICU patients are often sedated. Sedation relieves stress. On the other hand, the literature suggests that the healthcare providers' compassion can reduce post-discharge PTSD in critically ill patients [15]. The ICU staff are more compassionate. These might explain the lower incidence of PTSD among the non-ICU admitted survivors.

A 3-month follow-up study conducted by Salem et al. demonstrated that half of the COVID-19 survivors had restrictive lung impairment on PFT [16]. An 8-month follow-up study reported FEV_1/FVC abnormality in 20% of participants, of whom 5% (two patients) had a history of chronic obstructive pulmonary disease (COPD) with a significant history of cigarette smoking [17]. Our findings are in line with a recent meta-analysis reporting a 15% overall prevalence of restrictive patterns [18]. Impaired peak expiratory flow rate and FEF 25–75% indicated small airway obstruction. A high prevalence of small airway obstruction is reported, similar to pervious literature [17]. Autopsies of COVID-19 patients have shown destructed alveolar structure and pulmonary interstitial fibrosis [18].

The most frequent ECG findings are bradycardia, conduction block, and ST-T wave changes. Persistent cardiovascular injury is suspected as the ECG abnormalities are observed in a significant proportion of recovered patients upon a 1-year follow-up [19]. On echocardiography, LV systolic dysfunction was only observed in the ICU-admitted survivors. LV diastolic dysfunction was more frequent in the ICU-admitted patients. This study is in line with a 4-month follow-up study reporting a lower ejection fraction than 50% in 10% of ICU-admitted patients [20].

This study shows a significant number of COVID-19 survivors had sequelae after 6 months of discharge, the most frequently psychological and pulmonary sequelae. Based on the experience with SARS and MERS, more extended follow-up studies are necessary. Future studies should consider the COVID-19 treatment received for each patient while assessing the disease's long-term impact.

Strengths

The study population consisted of patients without comorbidity, so our findings are primarily suggestive of COVID-19 sequelae rather than exacerbation of the comorbid disease. We studied multiple organ systems in this comprehensive study.

Limitations

The first main limitation of this study was the small sample size. Low response rate is another limitation. Many patients had a bad experience during hospitalization and declined to come back for follow-up; underestimating the PTSD rate in COVID-19 survivors should be considered. We recruited control group from hospital staff who had no history of flu-like symptoms, cough, dyspnea, or confirmed COVID-19 diagnosis. Due to the occupational environment, the mental health of the control group is not the same as the general population, especially during the pandemic. Therefore, the long-term impact of COVID-19 on mental health may be even more prominent.

Conclusion

Many of the COVID-19 survivors may experience anxiety, fatigue, and PTSD. Pulmonary function might be impaired in some survivors. These post-recovery complications are noted up to 6 months after discharge. Further follow-up studies should be conducted to investigate the long-term complications.

Abbreviations

COVID-19	Coronavirus disease 2019
HIS	Hospital information system
PTSD	Post-traumatic stress disorder
CT	Computed tomography
PFT	Pulmonary function test
TDI	Tissue doppler imaging
ECG	Electrocardiogram

LVEDD	Left ventricular end-diastolic diameter
LVESD	Left ventricular end-systolic diameter
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-PCR	Real-time reverse transcriptase polymerase-chain-reaction
BFI	Brief fatigue inventory
PCL	Post-traumatic stress disorder checklist
SF-36	36-Item short-form survey
PCL-C	Post-traumatic stress disorder checklist for civilians
DSM-IV	Diagnostic and statistical manual of mental disorders
HAMA	Hamilton anxiety scale
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
FEF25-75%	Forced mid-expiratory flow
PEF	Peak expiratory flow
CPK-MB	Creatine kinase myocardial band
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
CBC	Complete blood count
IQR	Interquartile range
BMI	Body mass index
AST	Aspartate transaminase
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
TSH	Thyroid stimulating hormone
FBS	Fasting blood sugar
HbA1C	Hemoglobin A1C
ICU	Intensive care unit
LDH	Lactate dehydrogenase
HRQoL	Health related quality of life
GGO	Ground-glass opacities
LVEF	Left ventricle ejection fraction
GLS	Global longitudinal strain
MERS	Middle East respiratory syndrome
COPD	Chronic obstructive pulmonary disease

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Authors' contributions
NSH and HR came up with the idea, and HR, MHMB, and FB designed the study. NSH, MHMB, FZ, ED, MS, ZK, MN, AZ, HDH, HK, ZKH, MD, AS, MRK, and AB collected the data. HR and NSH analyzed the data. All authors have drafted the paper. Also, all authors critically revised the manuscript for important intellectual content and gave final approval for the version to be published.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
The ethics committee of Alborz University of Medical Sciences approved the study protocol . The written informed consent was obtained from all the participants.

Competing interests
The authors declare that they have no competing interests.

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