Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Medicine 174 (2020) 106197

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Follow up of patients with severe coronavirus disease 2019 (COVID-19): Pulmonary and extrapulmonary disease sequelae

Ayham Daher [a,*], Paul Balfanz [b], Christian Cornelissen [a], Annegret Müller [a], Ingmar Bergs [a], Nikolaus Marx [b], Dirk Müller-Wieland [b], Bojan Hartmann [b], Michael Dreher [a,1], Tobias Müller [a,1]

[a] Department of Pneumology and Intensive Care Medicine, University Hospital RWTH Aachen, Aachen, Germany
[b] Department of Cardiology, Angiology and Intensive Care Medicine, University Hospital RWTH Aachen, Aachen, Germany

ARTICLE INFO

Keywords:
COVID-19
Follow up
Pulmonary functions
Echocardiography
Quality of life
Fatigue

ABSTRACT

Background: Since December 2019 the novel coronavirus disease 2019 (COVID-19) has been burdening all health systems worldwide. However, pulmonary and extrapulmonary sequelae of COVID-19 after recovery from the acute disease are unknown.

Material and methods: Hospitalized COVID-19 patients not requiring mechanical ventilation were included and followed 6 weeks after discharge. Body plethysmography, lung diffusion capacity (DLco), blood gas analysis (ABG), 6-min walk test (6MWT), echocardiography, and laboratory tests were performed. Quality of life (QoL), depression, and anxiety were assessed using validated questionnaires.

Results: 33 patients with severe disease were included. Patients were discharged without prophylactic anticoagulation. At follow-up there were no thromboembolic complications in any patient. 11 patients (33%) had dyspnea, 11 (33%) had cough, and 15 (45%) suffered from symptoms of fatigue. Pulmonary function tests including ABG did not reveal any limitations (TLC: median=94% of predicted {IQR:85-105}; VC: 93% {78-101}; FEV1: 95% {72-103}; FEV1/FVC 79% {76-85}; PaO2: 72 mmHg {67-79}; PaCO2: 38 mmHg {35-38}), except for slightly reduced DLco (77% {69-95}). There were no echocardiographic impairments. 6MWT distance was reduced in most patients without oxygen desaturation. According to standardized questionnaires, patients suffered from reduced QoL, mainly due to decreased mobility (SGRQ activity score: 54 {19-78}). There were no indicators for depression or anxiety (PHQ-9: 7 {4-11}, GAD-7: 4 {1-9}, respectively).

Conclusions: Hospitalized patients with severe COVID-19, who did not require mechanical ventilation, are unlikely to develop pulmonary long-term impairments, thromboembolic complications or cardiac impairments after discharge but frequently suffer from symptoms of fatigue.

1. Introduction

Since December 2019 a novel coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been causing a rapidly spreading international outbreak; which has been burdening all health systems over the globe through a new form of pneumonia called coronavirus disease 2019 (COVID-19) [1–3]. Although the majority of infected patients has asymptomatic infection or mild disease [4–8]; the overall numbers of severe cases and the fatality rates are unfortunately high [8–10]. Additionally, the

Abbreviations: ABG, arterial blood gas; COVID-19, coronavirus disease 2019; DLco, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAD-7, Generalized Anxiety Disorder 7; IQR, Interquartile range; 6MWT, 6-min walk test; PaCO2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PFTs, pulmonary function tests; PHQ-9, Patient Health Questionnaire 9; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGRQ, St. George's Respiratory Questionnaire; SpO2, oxygen saturation on pulse oximeter; TLC, total lung capacity; VC, vital capacity; VTE, venous thromboembolism; V/Q scan, ventilation/perfusion scan.

* Corresponding author. Department of Pneumology and Intensive Care Medicine, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074, Aachen, Germany.

E-mail addresses: adaher@ukaachen.de (A. Daher), pbalfanz@ukaachen.de (P. Balfanz), ccornelissen@ukaachen.de (C. Cornelissen), amueller@ukaachen.de (A. Müller), ibergs@ukaachen.de (I. Bergs), nmarx@ukaachen.de (N. Marx), dirmueller@ukaachen.de (D. Müller-Wieland), bhartmann@ukaachen.de (B. Hartmann), mdreher@ukaachen.de (M. Dreher), tobmueller@ukaachen.de (T. Müller).

[1] Contributed equally.

https://doi.org/10.1016/j.rmed.2020.106197
Received 27 July 2020; Received in revised form 8 October 2020; Accepted 19 October 2020
Available online 20 October 2020

complication rates as well as extrapulmonary organ involvement (e.g. thromboembolic complications, cardiac and neurological involvement) are apparently higher in patients suffering from COVID-19 compared to other acute respiratory diseases [11–20]. Furthermore, even asymptomatic patients may have objective abnormalities, like ground-glass opacities on computed tomography (CT) and disturbances in gas exchange [21,22].

Recovery time from the acute disease appears to be around two weeks in mild and three to six weeks in severe disease [23], though there is not enough information about the possible sequelae after recovery from acute disease. An analysis of 110 survivors with COVID-19 showed impairments in diffusing capacity for carbon monoxide (DLco) and some restrictive ventilatory defects at the time of discharge from hospital [24], whereas the clinical relevance and the course of these abnormalities following discharge, and their impact on quality of life have not been studied so far. A systematic review and meta-analysis of the literature on patients with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) after hospitalization showed impaired DLco and reduced exercise capacity (6-min walking distance) at 6 months with limited improvement beyond that [25]. Furthermore, survivors of SARS and MERS had a considerable prevalence of psychological impairments such as post-traumatic stress disorder (PTSD), depression, anxiety and reduced quality of life beyond 6 months [25]. However, such testing has not been performed in patients with COVID-19 yet, although this could provide a better understanding of this emerging disease and could help to ensure an adequate and timely management of significant health limitations with the aim of restoring premorbid quality of life [25].

The aim of this study was to investigate pulmonary impairments, as well as the prevalence of other organ dysfunctions and psychological disorders in patients with COVID-19 six weeks after discharge from hospital.

2. Methods

2.1. Patient population

The present prospective study included 33 consecutive patients who had been hospitalized due to COVID-19 confirmed by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) in a respiratory tract sample. All patients were admitted to the isolation ward between February and May 2020. Only symptomatic patients with severe disease needing hospitalization were included. We excluded patients with Acute Respiratory Distress Syndrome (ARDS) who needed mechanical ventilation in the intensive care unit (ICU) during their stay. At discharge, patients got routine follow-up appointments in the pulmonary disease outpatient clinic six weeks after discharge.

The protocol for this study was approved by the local ethics committee (EK 080/20). All investigations were performed in accordance with the ethical standards laid down in the Declaration of Helsinki in its latest revision. Written informed consent was obtained from all patients prior to inclusion.

2.2. Assessment during hospital stay

Demographic data, disease history, coexisting medical conditions, presence of chronic respiratory failure, smoking history, and medication history were recorded for all patients (Table 1). Symptoms at admission and a detailed history of present symptoms were also documented.

Patients were assessed for eligibility on the basis of a positive RT-PCR assay for SARS-CoV-2 in a respiratory tract sample.

Transthoracic echocardiography was performed using a VIVID-E9 ultrasound machine (GE).

Serum, plasma, and whole blood samples were obtained routinely at the time of admission. Complete blood count, coagulation tests, inflammatory markers [like circulating levels of C-reactive protein (CRP), Procalcitonin (PCT), Ferritin, Interleukin-6 (IL-6)], N-terminal pro B-type natriuretic peptide, and creatinine levels in blood were measured among other tests (Table 2).

Table 1
Baseline characteristics and medical history.

	Patients (n = 33)
Age, years	64 ± 3
Female	11 (33%)
Comorbidities	
- COPD	3 (9%)
- Bronchial asthma	4 (13%)
- Hypertension	19 (59%)
- Heart failure	3 (9%)
- Arial fibrillation	3 (9%)
- Chronic kidney disease	7 (22%)
- Coronary artery disease	6 (19%)
- Diabetes mellitus	8 (25%)
Previous medications	
- ACE inhibitors	9 (26%)
- Beta blockers	8 (24%)
- Diuretics	14 (41%)
- Oral antihyperglycemic agents	8 (24%)
- Insulin	3 (9%)
- Antiplatelet therapy	7 (21%)
- Oral anticoagulants	3 (9%)
- Inhalation therapy	8 (24%)
- Nonsteroidal anti-inflammatory drugs (NSAIDs)	7 (21%)
Symptom onset to Hospitalization, days	6 ± 0.8
In-hospital Periods, days	
- Fever days	8 ± 1.0
- Hospitalization	15 ± 1.8
- Oxygen supplementation	9 ± 1.4
Time from discharge to follow-up, days	56 {48–71}

Values are presented as mean ± standard deviation, number of patients (percentage) or median {interquartile range}.
ABBREVIATIONS: ACE = angiotensin converting enzyme; COPD = chronic obstructive pulmonary disease.

2.3. Assessment at follow-up

At follow-up full pulmonary function tests (PFTs), electrocardiography, and transthoracic echocardiography were performed. Furthermore, blood samples were taken; and health-related quality of life was assessed. With support of a trained study team, patients answered different clinical questionnaires to assess various aspects of their quality of life including: Patient Health Questionnaire 9 (PHQ-9) of depression [26], Generalized Anxiety Disorder 7 (GAD-7) [27], St. George's Respiratory Questionnaire (SGRQ) (which is scaled from 0 representing optimal health to 100 reflecting worst health, and has three main components: symptoms component evaluates respiratory symptoms; activities component evaluates the physical activity; and the impacts component assesses social and psychological limitations) [28,29], and EQ-5D-5L (**E**uro **Q**uality of life - **five D**imensions - **five L**evels) questionnaire, which is a descriptive system that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression [30].

Whole-body plethysmography (MasterLab; Viasys, Hoechberg, Germany) was performed before and after bronchodilation (including DLco measurement only after bronchodilation) according to current guidelines and recommendations [31,32]. Samples for blood gas analyses (ABG) were taken from the arterialized earlobes of all patients while breathing room air without supplemental oxygen (ABL 800 flex; Radiometer, Copenhagen, Denmark).

All patients underwent 6-min walk test (6MWT) without supplemental oxygen, with measurements of vital parameters including oxygen saturation on pulse oximeter (SpO2) and Borg-scale before and after

Table 2
Laboratory findings.

	Reference values	Admission day (n = 33)	Follow up (n = 33)
Hematology			
- White blood cells, × 10^9/L	*4.0–10.0*	6.9 {5.1–7.9}	6.5 {5.6–7.4}
- Hemoglobin, g/dl	*m: 14.0-18.0 w: 12.0-16.0*	13.9 {11.8–14.9}	13.6 {11.7–14.5}
- Platelets, × 10^9/L	*150–400*	205 {164–241}	262 {202–303}
- Lymphocytes, %	*22.0–53.0*	11.9 {9.4–21.0}	26.7 {20.6–33.8}
- Eosinophils, %	*1.0–6.0*	0.1 {0–0.2}	2.1 {1.4–3.0}
Coagulation			
- INR		1.2 {1.1–1,2}	1 {0.9–1.2}
- aPTT, sec.	*25.1–36.5*	27.2 {25.2–29.3}	29.0 {27.8–31.4}
- Antithrombin III, %	*80–120*	–	107 {96–114}
- Fibrinogen, mg/dl	*238–498*	–	342 {293–391}
- D-dimer, ng/ml	*< 500*	855 {739–873}	474 {323–675}
- Thrombin time, sec.	*10–17*	21 {17.4–24.5}	15 {14-16}
Clinical Chemistry			
- HbA1c, %	*< 5.7*	5.9 {5.5–6.8}	5.3 {5.0–6.1}
- Sodium, mmol/l	*136–145*	138 {136–141}	141 {139–143}
- Potassium, mmol/l	*3.6–5.5*	4.2 {3.8–4.7}	4.5 {4.3–4.7}
- Phosphate, mmol/l	*0.81–1.45*	–	0.97 {0.85–1.12}
- Cholesterol, mg/dl	*< 200*	145 {116–195}	177 {135–231}
- HDL-cholesterol, mg/dl	*> 45*	35 {30-40}	50 {45–55}
- LDL-cholesterol, mg/dl	*< 130*	86 {66–140}	118 {77–161}
- Triglycerides, mg/dl	*< 200*	109 {93–189}	140 {107–196}
- Lipoprotein (a), nmol/l	*< 75*	–	23 {9-32}
- Albumin, g/dl	*3.5–5.2*	3.8 {3.5–4.2}	4.3 {4.1–4.6}
- Bilirubin (total), mg/dl	*< 1.2*	0.6 {0.5–0.6}	0.43 {0.29–0.67}
- AST, U/l	*< 35*	48 {32–60}	24 {20-29}
- ALT, U/l	*< 35*	29 {22-40}	24 {17-39}
- Gamma-GT, U/l	*< 40*	29 {22–84}	30 {17–46}
- AP, U/l	*35–105*	64 {50–82}	74 {56–85}
- LDH, U/l	*m: 135-225 w: 135-214*	324 {258–438}	213 {196–227}
- CK, U/l	*m: < 174 w: < 140*	129 {82–337}	84 {49–109}
- CK-MB-Mass, U/l	*< 26 U/l*	–	2 {1.5–3.0}
- hs-Troponin T, pg/ml	*< 14.0*	21 {9–140}	8 {4-21}
- NT-proBNP, pg/ml	*< 220*	147 {27–710}	183 {43–474}
- Urea, mg/dl	*16.6–48.5*	32 {23-42}	36 {28–47}
- Creatinine, mg/dl	*0.5–1.2*	1 {0.8–1.1}	0.88 {0.79–1.13}
- CRP, mg/l	*< 5*	57.1 {20.9–103.1}	2.0 {1.1–7.9}
- Procalcitonin, ng/ml	*< 0.5*	0.1 {0.1–0.2}	0.05 {0.04–0.06}
Iron metabolism			
- Iron, µg/dl	*33–193*	–	79.3 {60.5–99.1}
- Transferrin saturation, %	*16.0–45.0*	–	20.4 {15.3–26.5}
- Ferritin, ng/ml	*15.0–150.0*	1140.5 {955–1196.8}	154.6 {81.8–362.8}
Proteins			
- Cystatin C, mg/l	*0.61–0.95*	–	1.03 {0.96–1.42}
- Myoglobin, µg/l	*25–58*	34 {34-34}	27 {21–55}
Thyroid parameters			
- TSH, mU/l	*0.27–4.20*	1.5 {1.1–1.8}	1.6 {1.1–2.2}
- fT3, ng/l	*2.0–4.4*	1.8 {1.7–2.4}	3.2 {2.7–3.4}
- fT4, ng/dl	*0.9–1.7*	1.2 {1.1–1.4}	1.1 {1.1–1.2}
Cytokines			
- sIL-2-receptor, U/ml	*158–623*	–	470 {401–602}
- IL-6, pg/ml	*< 7.0*	64.2 {38.5–106.9}	2.4 {1.5–3.9}
- TNF alpha, pg/ml	*< 8.1*	–	8.1 {5.8–9.8}

Values are median {interquartile range}.
ABBREVIATIONS: ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; CK = creatine kinase; CKmb = creatine kinase myocardial band; CRP = C-reactive protein; FT3 = unbound triiodothyronine; FT4 = unbound thyroxine; Gamma-GT = gamma-glutamyltransferase; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; hs-Troponin-T = high sensitive Troponin-T; IL-6 = interleukin-6; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; NT-proBNP = N-terminal pro B-type natriuretic peptide; sIL 2 = soluble interleukin-2 receptor; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone.

exercise according to current recommendations [33,34]. Differences to the walk distance predicted values and lower limit of normal values (lower 95% confidence interval) were calculated for all patients. All patients with elevated D-dimer levels underwent ultrasound duplex scanning and ventilation/perfusion (V/Q) scan to rule out venous thromboembolism (VTE).

2.4. Statistical analysis

Statistical analyses were performed using standard descriptive statistics including median {interquartile range}, quartiles, frequencies, and percentages (%).

3. Results

Between February and May 2020, a total of 57 patients with COVID-19 were discharged from the isolation ward. We describe the first 33 patients (age 64 ± 3, 67% male) being admitted to our outpatient clinic for follow-up examination six weeks after discharge from hospital. Baseline characteristics, laboratory findings and symptoms at admission day are described in Tables 1–3 respectively. All 33 patients had a severe disease during their hospital stay, of which 27 (82%) had hypoxemic respiratory failure and needed supplemental oxygen therapy. 25 patients (76%) had bilateral opacities, and two patients (6%) had unilateral opacities on radiographic examinations. Three patients suffered from Chronic obstructive pulmonary disease (COPD) according to their medical history, one of them was on long-term oxygen therapy (LTOT) previously. Another four patients had a medical history of bronchial asthma. Four other patients had been diagnosed with chronic heart failure previously, two of them had reduced left ventricular ejection fraction (LVEF) and the other two had reduced left and right ventricular ejection fraction (RVEF). Only three patients had been put on oral anticoagulant therapy before admission due to atrial fibrillation and a medical history of ischemic stroke respectively. Apart from these patients, all patients were discharged without anticoagulants.

At hospital admission, patients had increased D-dimer levels (median = 855 ng/ml {IQR: 739–873}), an increased serum lactate dehydrogenase (LDH) activity (median = 324 U/L {IQR: 258–438}), as well as high inflammatory parameters (CRP, ferritin, and IL-6) (Table 2). At the time of follow up (56 days after discharge in median {IQR: 48–71}), the abovementioned laboratory parameters were mostly in the normal range (Table 2). Ferritin and IL6 declined to normal values in all patients. Although median D-dimer was not elevated, some patients had elevated values and underwent ultrasound duplex scanning and V/Q scan, excluding VTE in all patients. Of the 33 patients, 11 (33%) suffered from cough and had dyspnea and 15 (45%) had fatigue symptoms. Importantly, on average PFTs including ABG revealed no impairments (TLC: median = 94% of predicted {IQR 85–105}; VC: 93% {78–101}; FEV1: 95% {72–103}; FEV1/FVC: 79% {76–85}; PaO2: 72 mmHg

Table 3
Symptoms and diagnostic findings.

	Admission day (n = 33)	Follow up (n = 33)
Symptoms		
- Fever	22 (67%)	1 (3%)
- Cough	23 (70%)	11 (33%)
- Dyspnea	16 (48%)	11 (33%)
- Fatigue	21 (64%)	15 (45%)
- Tiredness	18 (55%)	15 (45%)
- Hemoptysis	1 (3%)	0 (0%)
- Rhinorrhea	2 (6%)	4 (12%)
- Sore throat	8 (24%)	3 (9%)
- Pharyngalgia	4 (12%)	0 (0%)
- Angina pectoris	4 (12%)	6 (18%)
- Myalgia	12 (42%)	5 (15%)
- Headache	7 (21%)	5 (15%)
- Cognitive disorders	–	6 (18%)
- Loss of Smell	8 (24%)	4 (12%)
- Loss of Taste	9 (27%)	3 (9%)
Gastrointestinal symptoms	17 (52%)	3 (9%)
- Diarrhea	13 (39%)	3 (9%)
- Nausea	8 (24%)	2 (6%)
- Emesis	2 (6%)	0 (0%)
- Stomach pains	7 (21%)	1 (3%)
Examination and vital parameters		
Height, cm	172 {165–178}	172 {165–178}
Weight, kg	83 {71–95}	83 {72–97}
BMI, kg/m^2	28 {24-31}	29 {24-31}
Respiratory rate, bpm	20 {18-23}	16 {15-18}
Oxygen saturation, %	94 {90–97}	98 {97–99}
Needing oxygen therapy, n (%)	27 (82%)	1 (3%)
Oxygen flow, l/min	0 {0–2}	–
Temperature, °C	38 {37-39}	36,6 {36,5-36,9}
Systolic BP, mmHg	126 {110–139}	140 {126–152}
Diastolic BP, mmHg	76 {66–80}	89 {79–100}
Heart rate, bpm	90 {80–102}	80 {72–89}
Frailty Score	–	3 {3-4}
Pulmonary function parameters and ABGs		
- TLC, % of predicted	–	94 {85–105}
- VC, % of predicted	–	93 {78–101}
- RV, % of predicted	–	112 {98–127}
- RV/TLC, % of predicted	–	109 {98–126}
- FEV1, % of predicted	–	95 {72–103}
- FEV1/FVC, %	–	79 {76–85}
- R eff, % of predicted	–	86 {62–104}
- DLCO, % of predicted	–	65 {53–73}
- DLCO/VA, % of predicted	–	77 {69–95}
ABG		
- paO 2, mmHg	–	72 {67_79}
- paCO 2, mmHg	–	38 {35_38}
- pH	–	7.4 {7.4_7.4}
- Base excess, mmol/l	–	0.8 {-0.6_+1.2}
- COHb, vol%	–	0.9 {0.7_1}
6MWT		
- Distance, m	–	380 {180_470}
- Distance < predicted value, n	–	26 (79%)
- Distance < LLN, n	–	15 (45%)
- Walk distance - predicted value, m	–	−138 {-37_-191}
- Walk distance - LLN, m	–	1.5 {-52_+130}
- SpO2 before exercise, %	–	97 {94_98}
- SpO2 after exercise, %	–	96 {94_98}
- HR before exercise, bpm	–	76 {61_86}
- HR after exercise, bpm	–	91 {74_100}
- Dyspnea on Borg scale before exercise	–	0 {0_2}
- Dyspnea on Borg scale after exercise	–	1 {0_4}
- Fatigue on Borg scale before exercise	–	1 {0_3}
- Fatigue on Borg scale after exercise	–	1 {0_4}
Echocardiography		
- LVEF - global normal	17/18 (94%)	29/33 (88%)
- LVEF, %	54 {42–55}	52 {50–52}
- RVEF - global normal	17/18 (94%)	31/33 (94%)
- TAPSE, mm	–	20 {18-23}
- RVEDD, mm	–	37 {33-40}
- RVSP + CVP, mmHg	–	25 {22-31}
Virologic diagnostic		
- SARS-CoV-2 RNA - positive	33 (100%)	0 (0%)
- SARS-CoV-2 IgG – positive	–	30 (91%)
- SARS-CoV-2 IgG (quant.)	–	7.9 {4.8–9.9}

Values are presented as number of patients (percentage) or median {interquartile range}.
ABBREVIATIONS: ABGs = arterial blood gases; BP = Blood pressure; CVP = central venous pressure; DLco = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity; HR = heart rate; IgG = immunoglobulin G; LLN = lower limit of normal, LVEF = left ventricular ejection fraction; PaCO2 = partial pressure of carbon dioxide; PaO2 = partial pressure of oxygen; Reff = effective specific resistance; RNA = ribonucleic acid; RV = residual volume; RVEDD = right ventricular end-diastolic dimension; RVEF = right ventricular ejection fraction; RVSP = right Ventricular Systolic Pressure; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO2, oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; TLC = total lung capacity; VA = alveolar volume; VC = vital capacity.

{67–79}; PaCO2: 38 mmHg {35-38}), except for a slightly reduced diffusion capacity/alveolar volume (DLco/VA: median = 77% of predicted {IQR: 69–95}) (Table 3). Among the patients with pre-existing COPD, two had only a slightly impaired function test (GOLD I), whereas the third patient was classified as GOLD III and had been on long-term oxygen therapy previously. In the 6MWT, 26 patients (79%) had walk distances under their age-adjusted predicted values, of whom 15 patients (46%) had walk distance values lower than the age-adjusted lower limits of normal (walk distance median = 380 m {IQR 180–470}, difference under the predicted value = 138 m {37–191}). However, there was no drop in oxygen saturation after exercise (SpO2 after exercise: median = 96% {IQR 94–98}). Echocardiography did not reveal deterioration of left or right ventricular function and there was no evidence of pulmonary hypertension on electrocardiogram (ECG) or in the echocardiography [Right Ventricular Systolic Pressure (RVSP): median = 25 mmHg + Central venous pressure (CVP) {IQR: 22–31}] (Table 3). There was no pericardial effusion in any patient.

According to PHQ-9 and GAD-7 questionnaires, patients mostly suffered from mild depression and anxiety (PHQ-9: median = 7 {IQR: 4–11}, GAD-7: median = 4 {IQR 1–9}, respectively). The SGRQ test showed mainly reduced physical activity (activity score median = 54 {IQR 19–78}). Using the EQ-5D-5L, patients reported slight to moderate problems with mobility, self-care (washing or dressing), doing usual activities, pain/discomfort and anxiety/depression (Table 4). Quality of life scores at admission and follow up were available in 6 patients (Table 5). At admission, patients reported mainly moderate to severe problems with their mobility and severe pain/discomfort. At follow up, a slight to moderate level of limitation was documented.

4. Discussion

The present case series describes follow-up data of patients with severe COVID-19 six weeks after discharge from hospital. Although patients in our cohort had some respiratory symptoms, they had no significant ventilatory limitations in the PFTs and only a mild reduction in diffusing capacity of the lungs for carbon monoxide. In the echocardiography there were no abnormalities of cardiac function or wall movement disorders, and no indicators of pulmonary hypertension. In addition, there were relevant limitations of the walk distance during

Table 4
Questionnaires at follow up.

	Follow up (N = 33)
PHQ-9	7 {4-11}
GAD-7	4 {1-9}
SRGQ	
Symptoms Score	34 {9–57}
Activity Score	54 {19–78}
Impacts Score	12 {2-33}
Total Score	26 {7-42}
EQ-5D-5L	
Mobility (walking)	2 {1-3}
Self-Care	1 {1-1}
Usual Activities	2 {1-3}
Pain/Discomfort	2 {1-3}
Anxiety/Depression	2 {1-2}
EQ VAS	63 {53–80}

Values are median {interquartile range}.
ABBREVIATIONS: EQ-5D-5L = Euro quality of life - five dimensions - five levels; GAD-7 = generalized anxiety disorder 7; PHQ-9 = patient health questionnaire 9, SGRG = St. George's respiratory questionnaire.

Table 5
Questionnaires at admission and at follow up in 6 patients.

	Admission day (N = 6)	Follow up (N = 6)
PHQ-9	13{9-16}	8 {7-9}
GAD-7	8 {4-11}	5 {2-8}
SRGQ		
Symptoms Score	61 {49–75}	46 {42–63}
Activity Score	84 {65–87}	60 {54–93}
Impacts Score	27 {19-44}	22 {9-35}
Total Score	49 {43–58}	37 {25–47}
EQ-5D-5L		
Mobility (walking)	3 {3-3}	1 {1-4}
Self-Care	2 {2-2}	1 {1-1}
Usual Activities	3 {2-3}	3 {2-3}
Pain/Discomfort	4 {4-4}	2 {2-4}
Anxiety/Depression	2 {1-3}	2 {1-2}
EQ VAS	65 {58–83}	60 {50–70}

Values are median {interquartile range}.
ABBREVIATIONS: EQ-5D-5L = Euro quality of life - five dimensions - five levels; GAD-7 = generalized anxiety disorder 7; PHQ-9 = patient health questionnaire 9, SGRG = St. George's respiratory questionnaire.

exercise testing, but without exercise induced desaturation. Importantly, there were no thromboembolic events in our cohort of patients not receiving any anticoagulants. However, a significant number of patients reported to have fatigue symptoms and a low physical activity.

Autopsy data on patients who had died from COVID-19 showed different degrees of diffuse alveolar damage (DAD), with some early organization, however without marked fibrosis [35,36]. Nevertheless, it is still unclear if this lung damage leaves prolonged lesions in the lung tissue, and how relevant these abnormalities are on the long term. A recent study reported some limitation in PFTs (mainly decrease in the values of DLco) in patients with COVID-19 at 30 days after discharge [37]. Importantly, some of these patients had very severe disease during their hospital stay and suffered not only from isolated pneumonia, but also from the different burdens of mechanical ventilation (e.g. ventilator-induced lung injury), making them prone to all sequelae of critical illness. In contrast, patients requiring mechanical ventilation were excluded in our study to eliminate presumed effects of prolonged ventilation on the short-term follow-up outcomes; and they were evaluated after a longer period of time following discharge. Interestingly, despite the high prevalence of radiological pulmonary opacities at admission to hospital, there were no relevant limitations in the PFTs at the follow-up; even the diffusion capacity was only slightly reduced. Furthermore, no exercise-induced disturbances in gas exchange were observed. Taken together, COVID-19 per se seems not to cause prolonged pulmonary abnormalities after recovery from the acute disease which is in accordance with data from autopsy studies showing the absence of organizing interstitial fibrosis as well as other fibrotic changes even in patients suffering from ARDS associated with COVID-19 and in contrast to ARDS of different etiology [35,36,38]. However, whether the slightly reduced DLco reflects mild fibrosis at least in some patients cannot be answered by the data obtained in our study and should be further investigated at a later time point by pulmonary function test and imaging.

Another important finding of our follow-up analysis was that different aspects in quality of life were altered in patients after recovery from COVID-19. There was a significant tendency among the patients to suffer from fatigue symptoms with significant limitations of their mobility, which was also reflected by reduced 6MWT distance. Similar observations have been made during previous coronavirus outbreaks. In the 2003 SARS epidemic in Toronto, 10% of the survivors suffered from fatigue symptoms such as weakness, myalgia or headache three years later. Due to the severity of these symptoms, some patients were partly unable to carry out their previous job [39]. The explanation of these disturbances is uncertain, since there were no indicators of psychological trauma like depression or anxiety. One explanation could be the direct interaction of the novel Coronavirus with the central nervous system (CNS) and peripheral nervous system (PNS). It is now well known that there is a wide range of CNS and PNS involvement in COVID-19 [40]; and similar to other Coronaviruses, the novel virus may have caused chronic post-inflammatory CNS disturbances adversely affecting sleep, pain sensitivity, and energy which would lead to the development of fatigue syndrome [39]. Although some cardiac biomarkers were elevated at hospital admission, these values were regressive at follow-up after six weeks. A previous study showed that right ventricular function is often reduced among hospitalized COVID-19 patients [41]. However, after six weeks from discharge both left and right ventricular functions were preserved and there were no indicators of pulmonary hypertension, making a cardiac origin of the fatigue symptoms unlikely.

To the best of our knowledge, this is the first study to evaluate the risk of COVID-19-related thromboembolic diseases after recovery from the acute disease. Thromboembolic complications are quite common in severe cases, and the best marker of these complications is the D-dimer, which also has a good correlation with the severity of the disease and represents a good predictor for adverse outcomes [42–44]. In our cohort D-dimer levels were significantly elevated during active disease; with a drop at the time of follow-up. In the small fraction of patients with elevated D-dimer levels at follow-up, there was no evidence for thromboembolic diseases in the ultrasound duplex scanning and in V/Q scan. Major thrombotic events in patients with COVID-19 have been suggested as a possible cause of increased out-of-hospital sudden death episodes since COVID-19 outbreaks [43]. However, whilst this hypothesis needs to be further examined in bigger case-control studies, our findings suggest that the risk of thromboembolic complications is not increased in patients with COVID-19 being treated outside the ICU after discharge from hospital.

5. Conclusions

Hospitalized patients who suffered from severe COVID-19 and did not require mechanical ventilation are unlikely to develop long-term pulmonary and cardiac impairments or thromboembolic complications after discharge from hospital whereas fatigue is a common symptom.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Notation of prior abstract publication/presentation

No prior abstract publication/presentation to declare.

CRediT authorship contribution statement

Ayham Daher: Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Paul Balfanz:** Investigation, Data curation, Formal analysis. **Christian Cornelissen:** Investigation, Data curation. **Annegret Müller:** Investigation, Data curation. **Ingmar Bergs:** Investigation, Data curation. **Nikolaus Marx:** Resources, Investigation, Writing - review & editing. **Dirk Müller-Wieland:** Investigation, Writing - review & editing. **Bojan Hartmann:** Investigation, Data curation. **Michael Dreher:** Conceptualization, Project administration, Supervision, Validation. **Tobias Müller:** Conceptualization, Project administration, Supervision, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W.J. Liu, D. Wang, W. Xu, E. C. Holmes, G.F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (10224) (2020) 565–574.

[2] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C. L. Huang, H.D. Chen, J. Chen, Y. Luo, H. Guo, R.D. Jiang, M.Q. Liu, Y. Chen, X. R. Shen, X. Wang, X.S. Zheng, K. Zhao, Q.J. Chen, F. Deng, L.L. Liu, B. Yan, F. X. Zhan, Y.Y. Wang, G.F. Xiao, Z.L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.

[3] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.

[4] K. Mizumoto, K. Kagaya, A. Zarebski, G. Chowell, Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, Euro Surveill. 25 (10) (2020), 2020.

[5] A. Kimball, K.M. Hatfield, M. Arons, A. James, J. Taylor, K. Spicer, A.C. Bardossy, L.P. Oakley, S. Tanwar, Z. Chisty, J.M. Bell, M. Methner, J. Harney, J.R. Jacobs, C. M. Carlson, H.P. McLaughlin, N. Stone, S. Clark, C. Brostrom-Smith, L.C. Page, M. Kay, J. Lewis, D. Russell, B. Hiatt, J. Gant, J.S. Duchin, T.A. Clark, M.A. Honein, S.C. Reddy, J.A. Jernigan, Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility - king county, Washington, march 2020, MMWR, Morb. Mortal. Wkly. Rep. 69 (13) (2020) 377–381.

[6] A. Sakurai, T. Sasaki, S. Kato, M. Hayashi, S.I. Tsuzuki, T. Ishihara, M. Iwata, Z. Morise, Y. Doi, Natural history of asymptomatic SARS-CoV-2 infection, N. Engl. J. Med. 383 (9) (2020) 885–886.

[7] S. Tabata, K. Imai, S. Kawano, M. Ikeda, T. Kodama, K. Miyoshi, H. Obinata, S. Mimura, T. Kodera, M. Kitagaki, M. Sato, S. Suzuki, T. Ito, Y. Uwabe, K. Tamura, Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis, Lancet Infect. Dis. 20 (9) (2020) 1043–1050.

[8] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention, Jama 323 (13) (2020) 1239–1242.

[9] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, D.P. Barnaby, L.B. Becker, J.D. Chelico, S.L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z.M. Kozel, L.M. Marrast, J. N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area, Jama 323 (20) (2020) 2052–2059.

[10] J.A. Lewnard, V.X. Liu, M.L. Jackson, M.A. Schmidt, B.L. Jewell, J.P. Flores, C. Jentz, G.R. Northrup, A. Mahmud, A.L. Reingold, M. Petersen, N.P. Jewell, S. Young, J. Bellows, Incidence, clinical outcomes, and transmission dynamics of severe coronavirus disease 2019 in California and Washington: prospective cohort study, BMJ 369 (2020) m1923.

[11] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China, Jama 323 (11) (2020) 1061–1069.

[12] T. Chen, D. Wu, H. Chen, W. Yan, D. Yang, G. Chen, K. Ma, D. Xu, H. Yu, H. Wang, T. Wang, W. Guo, J. Chen, C. Ding, X. Zhang, J. Huang, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study, BMJ 368 (2020) m1091.

[13] M. Arentz, E. Yim, L. Klaff, S. Lokhandwala, F.X. Riedo, M. Chong, M. Lee, Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state, Jama 323 (16) (2020) 1612–1614.

[14] J. Cao, W.J. Tu, W. Cheng, L. Yu, Y.K. Liu, X. Hu, Q. Liu, Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in wuhan, China, Clin. Infect. Dis. (2020).

[15] G.B. Danzi, M. Loffi, G. Galeazzi, E. Gherbesi, Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur. Heart J. 41 (19) (2020) 1858.

[16] Y. Zhang, M. Xiao, S. Zhang, P. Xia, W. Cao, W. Jiang, H. Chen, X. Ding, H. Zhao, H. Zhang, C. Wang, J. Zhao, X. Sun, R. Tian, W. Wu, D. Wu, J. Ma, Y. Chen, D. Zhang, J. Xie, X. Yan, X. Zhou, Z. Liu, J. Wang, B. Du, Y. Qin, P. Gao, X. Qin, Y. Xu, W. Zhang, T. Li, F. Zhang, Y. Zhao, Y. Li, S. Zhang, Coagulopathy and antiphospholipid antibodies in patients with covid-19, N. Engl. J. Med. 382 (17) (2020) e38.

[17] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China, JAMA Neurol. 77 (6) (2020) 1–9.

[18] F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F. H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (2020) 145–147.

[19] T.J. Oxley, J. Mocco, S. Majidi, C.P. Kellner, H. Shoirah, I.P. Singh, R.A. De Leacy, T. Shigematsu, T.R. Ladner, K.A. Yaeger, M. Skliut, J. Weinberger, N.S. Dangayach, J.B. Bederson, S. Tuhrim, J.T. Fifi, Large-vessel stroke as a presenting feature of covid-19 in the young, N. Engl. J. Med. 382 (20) (2020), e60.

[20] G. Toscano, F. Palmerini, S. Ravaglia, L. Ruiz, P. Invernizzi, M.G. Cuzzoni, D. Franciotta, F. Baldanti, R. Daturi, P. Postorino, A. Cavallini, G. Micieli, Guillain-barré syndrome associated with SARS-CoV-2, N. Engl. J. Med. 382 (26) (2020) 2574–2576.

[21] Y. Wang, Y. Liu, L. Liu, X. Wang, N. Luo, L. Li, Clinical outcomes in 55 patients with severe acute respiratory syndrome coronavirus 2 who were asymptomatic at hospital admission in shenzhen, China, J. Infect. Dis. 221 (11) (2020) 1770–1774.

[22] Z. Hu, C. Song, C. Xu, G. Jin, Y. Chen, X. Xu, H. Ma, W. Chen, Y. Lin, Y. Zheng, J. Wang, Z. Hu, Y. Yi, H. Shen, Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China, Science China, Life Sci. 63 (5) (2020) 706–711.

[23] WHO Director-General's Opening Remarks at the Media Briefing on COVID-19 - 24 February 2020, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—24-february-2020 (Accessed June 26 2020).

[24] X. Mo, W. Jian, Z. Su, M. Chen, H. Peng, P. Peng, C. Lei, R. Chen, N. Zhong, S. Li, Abnormal pulmonary function in COVID-19 patients at time of hospital discharge, Eur. Respir. J. 55 (6) (2020).

[25] H. Ahmed, K. Patel, D. Greenwood, S. Halpin, P. Lewthwaite, A. Salawu, L. Eyre, A. Breen, R. O'Connor, A. Jones, M. Sivan, Long-term clinical outcomes in survivors of coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis of follow-up studies, 2020, 2020.04.16.20067975.

[26] K. Kroenke, R.L. Spitzer, J.B. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613.

[27] K. Kroenke, R.L. Spitzer, J.B. Williams, B. Löwe, The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review, Gen. Hosp. Psychiatr. 32 (4) (2010) 345–359.

[28] P.W. Jones, F.H. Quirk, C.M. Baveystock, The St george's respiratory questionnaire, Respir. Med. 85 (Suppl B) (1991) 25–31. ; discussion 33-7.

[29] P.W. Jones, F.H. Quirk, C.M. Baveystock, P. Littlejohns, A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire, Am. Rev. Respir. Dis. 145 (6) (1992) 1321–1327.

[30] R. Brooks, EuroQol: the current state of play, Health Pol. 37 (1) (1996) 53–72.

[31] J. Wanger, J.L. Clausen, A. Coates, O.F. Pedersen, V. Brusasco, F. Burgos, R. Casaburi, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. Macintyre, R. McKay, M.R. Miller, D. Navajas, R. Pellegrino, G. Viegi, Standardisation of the measurement of lung volumes, Eur. Respir. J. 26 (3) (2005) 511–522.

[32] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi, J. Wanger, Standardisation of spirometry, Eur. Respir. J. 26 (2) (2005) 319–338.

[33] A. Chetta, A. Zanini, G. Pisi, M. Aiello, P. Tzani, M. Neri, D. Olivieri, Reference values for the 6-min walk test in healthy subjects 20-50 years old, Respir. Med. 100 (9) (2006) 1573–1578.

[34] C. Casanova, B.R. Celli, P. Barria, A. Casas, C. Cote, J.P. de Torres, J. Jardim, M. V. Lopez, J.M. Marin, M. Montes de Oca, V. Pinto-Plata, A. Aguirre-Jaime, The 6-min walk distance in healthy subjects: reference standards from seven countries, Eur. Respir. J. 37 (1) (2011) 150–156.

[35] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 8 (4) (2020) 420–422.
[36] S. Tian, Y. Xiong, H. Liu, L. Niu, J. Guo, M. Liao, S.Y. Xiao, Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies, Mod. Pathol. 33 (6) (2020) 1007–1014.
[37] Y. Huang, C. Tan, J. Wu, M. Chen, Z. Wang, L. Luo, X. Zhou, X. Liu, X. Huang, S. Yuan, C. Chen, F. Gao, J. Huang, H. Shan, J. Liu, Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase, Respir. Res. 21 (1) (2020) 163.
[38] L.B. Ware, Autopsy in ARDS: insights into natural history, Lancet Respir. Med. 1 (5) (2013) 352–354.
[39] H. Moldofsky, J. Patcai, Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study, BMC Neurol. 11 (2011) 37.
[40] M.A. Ellul, L. Benjamin, B. Singh, S. Lant, B.D. Michael, A. Easton, R. Kneen, S. Defres, J. Sejvar, T. Solomon, Neurological associations of COVID-19, Lancet Neurol. 19 (9) (2020) 767–783.
[41] Y. Szekely, Y. Lichter, P. Taieb, A. Banai, A. Hochstadt, I. Merdler, A. Gal Oz, E. Rothschild, G. Baruch, Y. Peri, Y. Arbel, Y. Topilsky, The spectrum of cardiac manifestations in coronavirus disease 2019 (COVID-19) - a systematic echocardiographic study, Circulation 142 (4) (2020) 342–353.
[42] T. Iba, J.H. Levy, M. Levi, J. Thachil, Coagulopathy in COVID-19, J. Thromb. Haemostasis 18 (9) (2020) 2103–2109.
[43] T. Iba, J.H. Levy, J.M. Connors, T.E. Warkentin, J. Thachil, M. Levi, The unique characteristics of COVID-19 coagulopathy, Crit. Care 24 (1) (2020) 360.
[44] N. Tang, D. Li, X. Wang, Z. Sun, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia 18 (4) (2020) 844–847.