Exercise intolerance in post-COVID19 survivors after hospitalization

Online Data Supplement

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Material and Methods

Pulmonary function test and modified Medical Council Research (mMRC):

Pulmonary function test included spirometry (FVC, FEV1, FEV1/FVC), static lung volumes (TLC, RV) and diffusing capacity of lungs for carbon monoxide (DLCO and VA) were performed by using the Elite DX Body Plethysmography (MedGraphics, MGC, St Paul, MO, USA) with flow measurements carried out with a calibrated pneumotachograph (Pitot tube) and DLCO was measured by the modified Krogh technique (single breath)[13, 14].

The mMRC dyspnea scale was used as a self-assessment tool to measure the degree of breathlessness in activities of daily living on a scale from 0 to 4. Participants were categorized as having dyspnea by mMRC scale (1-4) or no dyspnea (0). [15]

Cardiopulmonary Exercise Testing (CPET)

The following measures were obtained: O_2 uptake (V'O_2, L/min), carbon dioxide (CO_2) output (V'CO_2, L/min), minute ventilation (V'E, L/min), the respiratory exchange ratio (RER, V'CO_2/V'O_2), end-tidal partial pressures for CO_2 (PETCO_2, mmHg) and O_2 (PETO_2, mmHg), respiratory rate (RR, breaths/min) and tidal volume (VT, L). The $_{PEAK}$V'O_2 was compared to previously established standards (22) and calculated according to the average of the last 20 seconds before peak exercise. The anaerobic threshold (AT) was identified using the modified V-slope method and confirmed with the ventilatory method (23). Delta V'E to ΔV'CO_2 ratio (ΔV'E/ΔV'CO_2) was calculated as a slope from the start of work rate (WR) to the respiratory compensation point (RCP). Reasons for considering a maximal test were a V'O_2 plateau; a RER $\geq$1.10; the peak of heart rate (HR) $\geq$ 85% pred or a rate of perceived exertion $\geq$ 5 on the Borg scale. An electrocardiogram was continuously monitored during CPET. Cuff systemic blood pressure at each 2 min and pulse oximetry (SpO_2%) were observed and recorded.
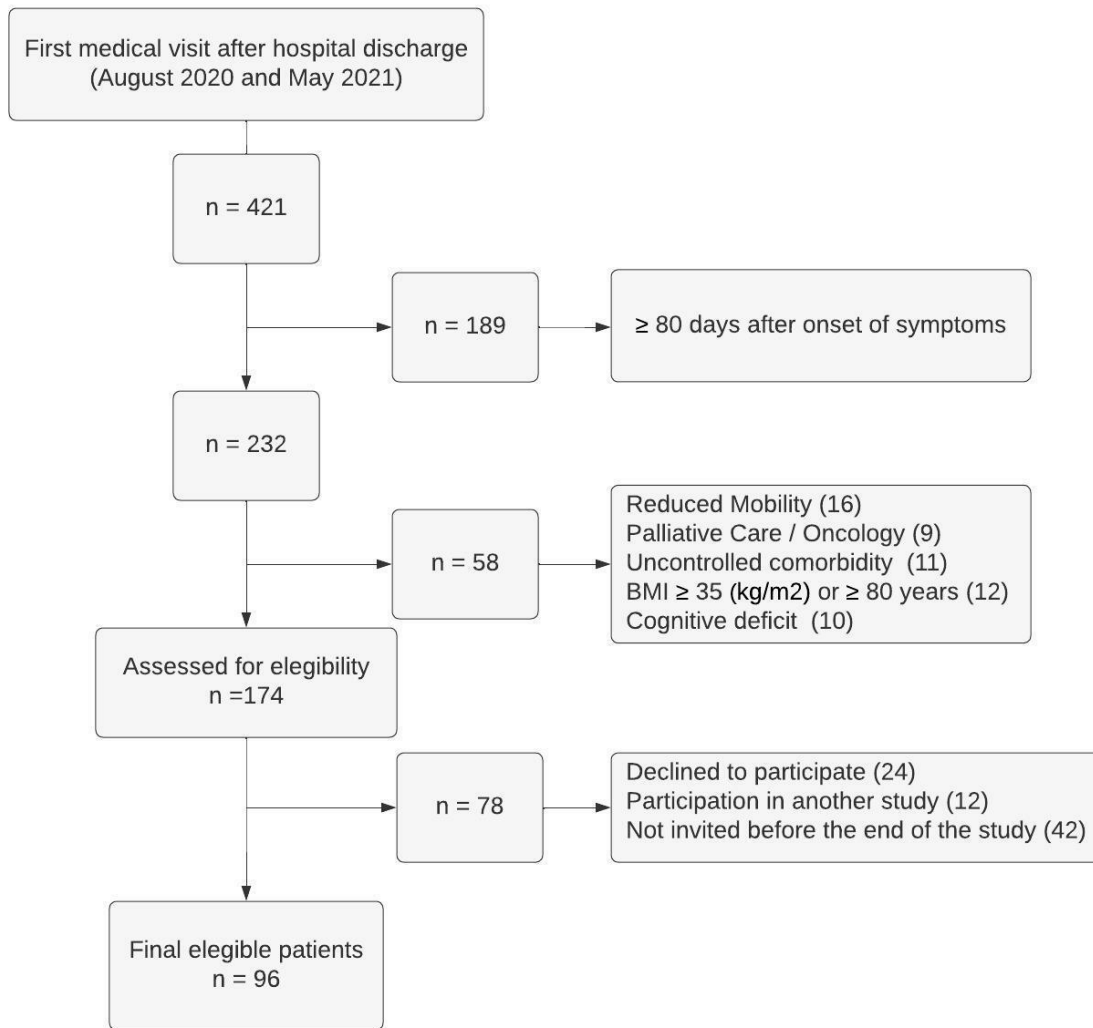
First medical visit after hospital discharge
(August 2020 and May 2021)

n = 421

n = 189 → ≥ 80 days after onset of symptoms

n = 232

n = 58 → Reduced Mobility (16)
Palliative Care / Oncology (9)
Uncontrolled comorbidity (11)
BMI ≥ 35 (kg/m2) or ≥ 80 years (12)
Cognitive deficit (10)

Assessed for elegibility
n =174

n = 78 → Declined to participate (24)
Participation in another study (12)
Not invited before the end of the study (42)

Final elegible patients
n = 96

Figure E1. Enrollment of patients at first medical visit after hospital discharge.

Table E1. Comorbidities, medications of continuous use and symptoms of hospital admission during hospitalization for COVID19.

Comorbidities	Total (n=87)	Acute symptoms at hospital admission	Total (n=87)
Systemic hypertension	45 (52)	Dyspnea	67 (77)
Ex-Smoker	29 (33)	Fever	61 (70)
Obesity	24 (28)	Cough	59 (68)
Diabetes	21 (24)	Myalgia	52 (60)
Hyperlipidemia	11 (13)	Headache	28 (32)
Asthma	8 (9)	Anosmia	27 (31)
Chronic kidney disease	8 (9)	Dysgeusia	20 (23)
Psychiatric diseases	9 (10)	Diarrhea	14 (16)
Kidney transplant	8 (9)	Nausea/Vomiting	12 (14)
No comorbidity	6 (7)	Fatigue	9 (10)
One comorbidity	25 (29)		
Chronic medications			
ARB/ACEi	37 (43)		
Oral hypoglycemic	20 (23)		
Diuretic	19 (22)		
Lipid-lowering agent	17 (20)		
Beta blockers	14 (16)		
Antiaggregant	11 (13)		
Antidepressants	9 (10)		
LABA+IC	7 (8)		
Insulin	6 (7)		
Immunosuppressants	3 (3)		
No medicine	21 (24)		

Data are presented as absolute value and percentage *(n %)*. A*bbreviation:* ARB: angiotensin-receptor blocker; ACEi: angiotensin-converting enzyme inhibitor; LABA: long-acting beta-agonists; IC: inhaled corticosteroids.

Table E2. Correlation coefficients for $_{PEAK}$ V'O$_2$ (ml/kg/min)

	r	p Values
$_{PEAK}$ V'O$_2$, ml/kg/min		
Age, yrs	-0.41	<0.001
Comorbidities, *n*	-0.41	<0.001
Hospitalized days, *n*	-0.07	0.511
Days in ICU, *n*	-0.10	0.485
Dyspnea, mMRC	-0.42	<0.001
FVC, % pred	0.25	0.029
DLCO, % pred	0.35	0.011
Peak V'E/MVV	0.38	<0.001
Peak VT, L	0.61	<0.001
Peak RR/VT	-0.36	<0.001
ΔV'E/ΔV'CO$_{2RCP}$	-0.45	<0.001
Peak VD/VT	-0.44	<0.001
Peak P(A-a)O$_2$, mmHg	-0.07	0.553
Peak P(a-ET)CO$_2$, mmHg	-0.35	0.003
Peak WR, watts	0.78	<0.001
ΔV'O$_2$/ΔWR, ml/min/watts	0.35	0.001
Peak Lactate, mmol/L	0.53	<0.001
Peak Lactate/WR, mmol/L/watts	-0.39	0.001
Peak CaO$_2$, mL/dL	0.30	0.012

Definition of abbreviation: ICU: intensive care unit; mMRC: modified Medical Research Council; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; V'E: minute ventilation; MVV: maximal voluntary ventilation; RR: respiratory rate; VT: tidal volume; CaO$_2$: oxygen content in arterial blood; P(A-a) O$_2$: alveolar-arterial oxygen difference; VD/VT: dead space fraction of tidal volume; P(a-ET)CO$_2$: arterial to End-tidal carbon dioxide difference; WR: work rate; PaCO$_2$: partial arterial pressure for carbon dioxide; PaO$_2$: arterial partial pressure of oxygen; Chest CT: percentage of lung parenchyma involvement. *The correlation is significant at the 0.05 level (2 ends); ** The correlation is significant at the 0.01 level (2 ends).

Table E3. Areas under the ROC curve for determining the cutoff for lung function and exercise variables for $_{PEAK}V'O_2 \leq 17.0$ml/kg/min.

	Cutoff values	Area under curve (%)	IC 95%	p - value
$_{PEAK}V'O_2 \leq 17.0$ml/kg/min				
mMRC	1	0.71	0.59 – 0.82	0.001
FVC, % pred	80	0.70	0.57 – 0.84	0.005
DLCO, % pred	65	0.75	0.59 – 0.92	0.004
Peak V'E/MVV	0.50	0.68	0.55 – 0.80	0.006
Peak RR/VT	40	0.70	0.58 – 0.82	0.002
$\Delta V'E/\Delta V'CO_{2RCP}$	32	0.74	0.63 – 0.85	<0.001
Peak VD/VT	29	0.80	0.68 – 0.91	<0.001
Peak P(a-ET)CO$_2$, (mmHg)	2.65	0.79	0.65 – 0.90	<0.001
Peak WR, watts	105	0.89	0.83 – 0.96	<0.001
$\Delta V'O_2/\Delta WR$, mL/min/watts	11.5	0.69	0.56 – 0.81	0.005
Peak Lactate, mmol/L	5.75	0.74	0.61 – 0.86	0.002
Peak Lactate/WR, (mmol/L/watts)	0.075	0.75	0.62 – 0.89	0.001
Peak CaO$_2$, mL/dL	21.5	0.67	0.52 – 0.82	0.025

Definition of abbreviation: mMRC: modified Medical Research Council; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; V'E: minute ventilation; MVV: maximal voluntary ventilation; RR: respiratory rate; VT: tidal volume; V'CO$_2$: carbon dioxide production; VD/VT: dead space fraction of tidal volume; P(a-ET)CO$_2$: arterial to End-tidal carbon dioxide difference; WR= work rate (watts).

Table E4. Multivariate logistic analysis adjusted for sex, age and any comorbidities for $_{PEAK}V'O_2 \leq$ 17.0 ml/kg/min according to persistence of symptoms, lung function and CPET variables.

Variables		MULTIVARIATE		
		p Values	Odds	IC
Symptoms	mMRC ≥ 1			
Lung Function	FVC ≤ 80, % pred	0.009	45.41	2.58 – 796.95
CPET				
Ventilatory responses	Peak RR/VT ≥ 40			
Gas-exchange responses	Peak VD/VT ≥ 29	0.007	53.91	3.02 – 962.81
Metabolic responses	Lactate/WR ≥ 0.075, mmol/L/watts			

Definition of abbreviation: mMRC: modified Medical Research Council; FVC: forced vital capacity; RR: respiratory rate; VT: tidal volume; VD/VT= dead space fraction of tidal volume; WR: work rate (watts). Multivariate logistic analysis corrects by age, sex and comorbidities, with $R^2 = 0.55$. Cutoff point of the variables defined by ROC Curve.