Cardiopulmonary Exercise Testing to Assess Persistent Symptoms at 6 Months in People With COVID-19 Who Survived Hospitalization – A Pilot Study

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Abstract

Objective. The aim of this pilot study was to assess physical fitness and its relationship with functional dyspnea in survivors of Covid-19, 6 months after their discharge from the hospital.

Methods. Data collected routinely from people referred for cardiopulmonary exercise testing (CPET) following hospitalization for Covid-19 were retrospectively analyzed. Persistent dyspnea was assessed using the modified Medical Research Council dyspnea (mMRC) scale.

Results: Twenty-three people with persistent symptoms were referred for CPET. Mean mMRC dyspnea score was 1 (SD = 1) and was significantly associated with VO2peak (%) (rho = -0.49). At 6 months, those hospitalized in the general ward had a slightly reduced VO2peak (87% [SD = 20]), whereas those who had been in the intensive care unit (ICU) had a moderately reduced VO2peak (77% [SD = 15]). Of note, the results of the CPET revealed that, in all patients, respiratory equivalents were high, power-to-weight ratios were low, and those who had been in the ICU had a relatively low ventilatory efficiency (mean VE/VCO2 slope = 34 [SD = 5]). Analysis of each individual showed that none had a breathing reserve <15% or 11L/min, all had a normal exercise electrocardiogram, and 4 had a heart rate above 90%.

Conclusion. At 6 months, persistent dyspnea was associated with reduced physical fitness. This study offers initial insights into the mid-term physical fitness of people who required hospitalization for Covid-19. It also provides novel pathophysiological clues about the underlaying mechanism of the physical limitations associated with persistent dyspnea. Those with persistent dyspnea should be offered a tailored rehabilitation intervention, which should probably include muscle reconditioning, breathing retraining, and perhaps respiratory muscle training.

Impact. This study is the first to show that a persistent breathing disorder (in addition to muscle deconditioning) can explain persistent symptoms 6 months after hospitalization for Covid-19 infection and suggests that a specific rehabilitation intervention is warranted.

[H1] Introduction

The Covid-19 virus causes serious infection, leading to hospitalization for many of those infected.[1] It is reasonable to assume that those who are admitted to hospital would experience cardiopulmonary complications[2] as well as muscle deconditioning due to isolation during hospitalization, which may be further complicated by intensive care unit acquired weakness (ICUAW). This has recently been highlighted by Van Aerde et al[3] and Belli et al[4] who both showed that people who survived Covid-19 infection had impaired physical fitness on discharge from hospital. However, the mid- and long-term impact of Covid-19 on physical fitness remains unknown, although cardiopulmonary impairments and symptoms, such as dyspnea or fatigue, may persist for months after discharge.[2,5] In addition, the field tests, such as those typically used during hospitalization[4] provide a non-specific evaluation of physical fitness that does not indicate the cause of the underlying limitation. As such it is difficult to implement specific, rehabilitation programs. The aim of this pilot study, therefore, was to assess physical fitness and its relationship with functional dyspnea in survivors of Covid-19, 6 months after discharge from the hospital and according to the mode of hospitalization in the general ward or in an ICU). The secondary aim was to assess the relationship between early clinical outcomes and physical fitness at 6 months. We hypothesized that physical fitness, assessed by peak oxygen uptake (VO2peak), would be markedly reduced (due to both a muscle deconditioning and pulmonary vascular or interstitial impairments related to the Covid-19 infection (12)), and would be related to functional dyspnea symptoms.

[H1] Methods

[H2] Design and patients

The Data collected routinely from people referred for a cardiopulmonary exercise testing (CPET) in Rouen University Hospital due to persistent symptoms (fatigue or dyspnea (5)) following hospitalization for Covid-19 were analyzed. The protocol was ethically approved by the Comité d'Ethique pour la Recherche sur Données Existantes et/ou hors loi Jardé, Rouen University Hospital (E2020-70). According to current French law, formal consent to retrospectively review medical records was not required. Patient data

confidentiality was respected and the protocol was performed in compliance with the Declaration of Helsinki.

[H2] *Assessment*

During a routine outpatient assessment 6 months post discharge, people underwent a comprehensive evaluation of respiratory function and physical fitness. This included an assessment of dyspnea using the mMRC dyspnea score, pulmonary function testing, respiratory muscle testing, arterial blood gas measurements and CPET. All these procedures were performed according to international guidelines,[6-8] adapted to limit the spread of the virus, and expressed as percent predicted values.[6,9-11]

Particularly, CPET was performed on an electromagnetic ergometer (Ergoline 900, GmbH, Bitz, Germany). After a 3-minute warm-up period, incremental ramp exercise (aimed to last for about 10 minutes using steps from 5 to 20 W/min depending on to the physician's evaluation, the patient's history and usual physical activity levels) was applied up to exhaustion. A face mask, pneumotach and gas analyzer (Vyntus CPX, Vyaire Medical, Mettawa, IL) were used to assess oxygen uptake (VO2) and carbon dioxide production (VCO2), breath by breath. VO2 measured during the last fully sustained ramp was defined as the VO2peak and was expressed as predicted value according to age, weight and sex. [8, 11-13] A VO2peak (% predicted value) below 85% was considered as clinically reduced.[8] For those people with obesity, a specific predictive equation was used instead to avoid any misinterpretation of a reduced VO2peak that would only be attributable to the obesity.[14] The corresponding cardiorespiratory variables and gas exchanges data were retrieved and expressed as percentages of predicted values.[11] Heart rate was continuously monitored with a 12-lead electrocardiogram, perceived exertion was assessed using the Borg scale[15] and arterial blood gases were measured at exhaustion (Suppl. Figure). The mechanisms of underlying the impairment in physical fitness were analyzed using mean or median values from the CPET at peak effort, separately according for each mode of hospitalization (general ward or ICU).[8,11]

Early clinical outcomes were also collected by through a retrospective chart review. These included initial pulmonary impairment measured from chest computed tomography (visually classified as normal, minimal (<10%), moderate (10%-25%), extensive (25%-50%),

very extensive (50%-75%) and critical (>75%) (16)), length of stay in ICU and in hospital, number of days of invasive mechanical ventilation (IMV), neuromuscular blockers, amine and extra-corporeal membrane oxygenation (ECMO) administration, number of sessions of active physical therapy, and the occurrence of acute respiratory distress syndrome (ARDS).

[H2] Statistical analysis

Descriptive statistics were reported as counts (percentages and 95% CI), means (SD) or medians (IQR) according to their distribution, which was assessed using the Kolmogorov-Smirnov normality test. In order to limit type 1 statistical errors, the analysis was restricted to the nine pre-specified early clinical outcomes, as well as dyspnea and potential physiological variables that contributed to a reduction in physical fitness. Physiological variables were restricted to those identified as potential contributors based on the interpretation of the CPET, pulmonary function testing and respiratory muscle testing results (ie, maximal inspiratory pressure, power to weight ratio, respiratory equivalents and minute ventilation to carbon dioxide slope), for a total of 14 analyses.

The relationship between VO2peak (%predicted value) and physiological variables and early clinical outcomes was assessed using a Pearson product correlation coefficient when the data met the requirements for linear analysis (ie, normally distributed and homoscedastic, assessed with Leven's test). The relationship between VO2peak (%predicted value) and data that did not meet the requirements for linear analysis were assessed using the Spearman rank order correlation test. The effect size of these relationships was expressed using by the correlation coefficient (r) and the Spearman rho respectively. Analysis relating to ICU and rescue therapy were undertaken on the overall cohort considering that those who were not been admitted to ICU had 0 days of the specific outcome. A sensitivity analysis was conducted specifically on the data of those admitted to ICU. Finally, the impact of categorical early clinical outcomes on VO2peak (% predicted value) was assessed using a Mann Whitney test (ARDS) or a Kruskal-Wallis test (initial scan). A *P* value of <.05 was considered as significant. GraphPad Prism 5.03 (GraphPad Software, San Diego, California, USA) and R 3.6.1 (The R Project for Statistical Computing, The R Foundation, r-project.org) were used for analyses.

[H1] Results

[H2] Patients

Twenty-four people were referred for CPET in our center up to November 2020. One was excluded because of a previous history of chronic respiratory failure with documented impairment of VO2peak (%). The remaining 23 people were aged on average 59 years (SD = 13), 48% were female and their mean body-mass index was 29kg/m² (SD = 4) (Tab. 1). None were provided with supplemental oxygen therapy. Their Covid-19 related outcomes are also shown in Table 2.

[H2] Cardiopulmonary exercise testing and relationship with dyspnea

The most frequent persistent symptom was dyspnea (78% [95% CI = 0.56 to 0.93]). The mean mMRC dyspnea score was 1 (SD 1) and was significantly associated with VO2peak (%) (rho = -0.49; *P* = .019) Figure 1A. Two people were treated with beta-blockers and five participated in regular active physical therapist sessions at the time of the outpatient assessment. At 6 months, 12 people (52% [95% CI = 0.33 to 0.71]) had a reduced VO2peak (%). Particularly, the VO2peak (87% [SD = 20]) of those hospitalized in the general ward was relatively preserved. It is worthy of note that their respiratory equivalent for oxygen (median 38 (IQR 30 to 42)) and carbon dioxide (mean = 33 [SD = 5]) were high, with a low power to weight ratio (mean = 1.5kg/w [SD = 0.6]) (17) (Tab. 3). Conversely, the mean VO2peak (%) of those admitted to ICU was moderately decreased (77% [SD = 15]) and was also associated with high respiratory equivalents for oxygen (median= 42 ; IQR = 31 to 43) and carbon dioxide (mean = 34 [SD = 4]), a relatively low ventilatory efficiency (mean VE/VCO2 slope = 34 [SD 5]) and a low power to weight ratio (mean = 1.3 W/kg [SD = 3]) (Table 3). Assessment of each individual showed that none had a breathing reserve <15% or 11 L/min, every all had a normal exercise electrocardiogram and four had a heart rate (%) above 90% (8). Finally, among the above-mentioned physiological variables, power to weight ratio was significantly related to VO2peak (%) (rho = 0.78; *P* < .001), and there was a tendency towards a relationship between VE/VCO2 slope and VO2peak (%) (rho = -0.39; *P* = .066) Figures 1B, 1C, and Table 3, 4.

[H2] *Association between early clinical outcomes and physical fitness*

Only one person underwent ECMO so this outcome was not further considered. There was no significant difference in VO2peak (%) at 6 months according to the level of pulmonary impairment seen on chest computed tomography (overall P = .366) Figure 2A nor between those people who experienced ARDS and those who did not (P = .131) Figure 2B. VO2peak (%) was not significantly associated with ICU length of stay (rho = -0.34; P = .111), duration of IMV (rho = -0.34; P = .108) or with the duration of curare (rho = -0.35; P = .106) or amine administration (rho = -0.34; P = .108) Figures 2C to 2F respectively. There was a trend toward an association with length of hospital stay (rho = -0.40; P = .058) and a significant relationship with the number of active inpatient physical therapist sessions (rho = -0.44; P = .040) Figures 1D and Figure 1E respectively. The sensitivity analysis including only those admitted to ICU is shown in Supplementary Table 1. Though the effect size was higher, none of the associations was were statistically significant.

[H1] Discussion

The results from this pilot study provide preliminary, reassuring signal about functional recovery 6 months following hospitalization for Covid-19. The results extend those of Sonnweber et al who showed recovered cardiopulmonary recovery function in people 3 months after a confirmed diagnosis of Covid-19.[18] A frequent persistent symptom, dyspnea,[15, 18] was significantly associated with a reduced physical fitness in the present study. Based on the results of the CPET, the persistent dyspnea is likely caused by both a persistent breathing disorder (overall high equivalents at VO2 peak and ventilatory inefficiency for those hospitalized in ICU) and muscle deconditioning. This deconditioning was evidenced by 1) an overall low power to weight ratio, 2) a non-identifiable ventilatory threshold in around 25% of the patients, and 3) for those with an identifiable threshold, VO2vt/VO2predicted was higher than 40% and no ventilatory or cardiac limitations were evident (11)). These data also suggest, contrary to our hypothesis, that pulmonary vascular or interstitial impairments (as assessed by the Vd/Vt ratio, P(A-a)O2, and arterial blood gases at exhaustion, see Tab. 3) were not major causes of mid-term impairment of physical fitness.

Another interesting finding was that physical fitness was not reduced due to ventilatory limitation. This might have been expected because those hospitalized in ICU had a more restrictive respiratory pattern and a reduced MIP. However, any clinically relevant impairment would have led to a reduced breathing reserve at exhaustion, which was not the case for any of those included. In contrast, ventilatory inefficiency may be involved in physical fitness impairment, particularly for those hospitalized in ICU (Fig. 1 and Tab. 3). In this context, This raises the question of whether inspiratory muscle training, in addition to muscle reconditioning, would be beneficial for those people with a reduced MIP. This issue warrants further evaluation because evidence from people with chronic obstructive pulmonary disease (COPD) suggests that it may not provide any further worthwhile clinical benefits, [19, 20] however the effect in the post-Covid-19 context is unknown.

There was a significant association between the number of active inpatient physical therapist sessions and VO2peak (% predicted value) in the mid-term (Fig. 1C). Although the negative nature of this relationship may be surprising at first glance, it probably reflects 1) that physiotherapists prioritized treatment of those with the highest levels of disability and 2) that the number of physical therapist sessions is influenced by length of hospital stay. This is corroborated by a trend toward an association between the total length of hospital stay and physical fitness 6 months following after discharge (Fig. 1B). Evidence from other populations, such as those with COPD, shows that hospitalization leads to physical inactivity (21) and muscle wasting.[22] Indeed, longer periods of hospitalization, which may in turn impact physical fitness 6 months later. The direct implication of these findings is that those people with long hospital stays should be closely followed up to determine their individual rehabilitation needs. Based on our results, we suggest that rehabilitation programs should include muscle reconditioning (including peripheral muscle strengthening and exercise training, similar to pulmonary rehabilitation), breathing retraining (23) and perhaps also respiratory muscle strengthening, to improve symptoms.

Though some studies in the field of ARDS reported an association between functional disability after hospital discharge and length of ICU stay,[24,25] we did not find such an association. This is likely due to the fact that this population was underrepresented in the present cohort (Fig. 2C).

[H2] *Limitations*

The main limit of this study is its small sample size: the results may not be representative of the whole population of Covid-19 survivors discharged from hospital. In addition, data should be interpreted cautiously because the presence of an outlier can lead to an overestimation of the relationship between variables or, conversely, actual but more modest relationship may be missed due to a lack of statistical power. Other limitations include the lack of evaluation of peripheral muscle strength and mood status (anxiety and depression). This prevented evaluation of the role of other non-physical potential contributors to physical fitness impairment, such as psychological status. In addition, no data were available about the physical fitness of the patients before Covid-19 infection nor at hospital discharge. Finally, those with the highest levels of disability may have not been referred for CPET during the 6 months-period following their discharge.

To conclude, this pilot study offers a preliminary insight into the mid-term physical fitness of people who survived Covid-19 and were discharged home. It also provides important novel pathophysiological clues regarding the mechanisms underlying of the physical limitations associated with persistent dyspnea. Finally, survivors of Covid-19 should be offered a tailored rehabilitation intervention. While this pilot study suggests a suitable rehabilitation intervention should include muscle reconditioning, breathing retraining and perhaps also respiratory muscle strengthening exercises, further studies are needed to identify the most effective rehabilitation approaches.

Author Contributions

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List of abbreviations

ARDS: Acute respiratory distress syndrome

CPET: Cardiopulmonary exercise testing

ECMO: Extra-corporeal membrane oxygenation

ICU: Intensive care unit

ICUAW: Intensive care unit acquires weakness

IMV: Invasive mechanical ventilation

$P(A-a)O_2$: Alveolar to arterial oxygen partial pressure gradient

VO_2: oxygen uptake

Vd/Vt ratio: ratio between dead space volume and volume tidal

Declarations

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Table 1. Clinical Characteristics at 6 Months in People With Covid-19 Who Survived Hospitalization [a]

Characteristics	People With Covid-19		
	Total Cohort (n = 23)	Survivors of General Ward (n = 16)	Survivors of ICU (n = 7)
Comorbidities, n (%)			
Respiratory condition (other than COPD)	6 (26)	4 (23)	2 (29)
COPD	1 (4)	0 (0)	1 (14)
Tobacco	9 (39)	8 (47)	1 (14)
Hypertension	9 (39)	6 (38)	3 (43)
Hypercholesterolemia	2 (9)	1 (6)	1 (14)
Diabetes	4 (17)	3 (18)	1 (14)
Cardiopathies	4 (17)	3 (18)	1 (14)
Obesity	11 (48)	7 (44)	4 (57)
CPAP-treated obstructive sleep apnea	4 (17)	3 (18)	1 (14)
Digestive condition	7 (30)	5 29)	2 (29)
Orthopedic	4 (17)	3 (18)	1 (14)
Cancer	0 (0)	0 (0)	0 (0)
Viral infection	2 (9)	0 (0)	2 (29)
Pulmonary function testing, mean (SD)			
FEV_1 *(L)*	3.1 (0.9)	3.2 (0.8)	2.9 (1.1)
FEV_1 *(%)*	104 (21)	109 (16)	92 (26)
FVC *(%)*	104 (22)	111 (18)	88 (21)
FEV_1/FVC *(%)*	0.80 (0.11)	0.80 (0.08)	0.80 (0.16)
VC *(%)*	103 (21)	109 (19)	87 (20)
RV *(%)*	90 (25)	91 (19)	88 (40)
TLC *(%)*	95 (16)	100 (12)	83 (19)
DLCO *(%)*	82 (16)	87 (11)	70 (21)
DLCO VA *(%)*	90 (14)	94 (13)	81 (14)
Arterial blood gas at rest			
PaO2 *(kPa),* mean (SD)	11.0 (1.7)	11.0 (1.7)	11.1 (1.7)
PaCO2 *(kPa),* mean (SD)	4.9 (0.5)	4.8 (0.3)	5.2 (0.7)
pH, mean (SD)	7.43 (0.03)	7.44 (0.03)	7.42 (0.02)
Hb *(g/dl),* mean (SD)	14 (2)	14 (2)	15 (1)
SaO2 *(%),* median (IQR)	97 (95 to 98)	97 (95 to 98)	97 (94 to 99)

HCO3- *(mmol/L)*, mean (SD)	25 (2)	25 (1)	25 (3)
P(A-a) O2 *(kPa)*, mean (SD)	2.9 (2.0)	3.2 (2.1)	2.5 (1.6)
Respiratory muscle testing			
MIP *(cm H2O)*, median (IQR)	51 (28 to 62)	54 (37 to 62)	28 (16 to 62)
MIP *(%)*, median (IQR)	73 (37 to 97)	87 (47 to 97)	42 (29 to 92)
MEP *(cm H2O)*, median (IQR)	63 (50 to 74)	65 (47 to 88)	60 (43 to 71)
MEP *(%)*, mean (SD)	78 (35)	78 (40)	78 (30)
SNIFF *(cm H2O)*, median (IQR)	80 (31)	83 (39)	79 (68 to 82)
SNIFF *(%)*, median (IQR)	100 (30)	107 (36)	87 (79 to 94)

[a] Percentages may not sum to 100 due to rounding. Abbreviations: COPD = chronic obstructive pulmonary disease; CPAP = constant positive airway pressure; DLCO = diffusing capacity of lung for carbon monoxide; DLCO VA = diffusing capacity of lung for carbon monoxide corrected for alveolar ventilation; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Hb = haemoglobin, MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; P(A-a)O2 = alveolar to arterial oxygen partial pressure gradient; PaO2 = arterial oxygen partial pressure; PaCO2 = arterial carbon dioxide partial pressure; RV = residual volume; SaO2 = arterial oxygen saturation; SNIIF = sniff test; TLC = total lung capacity; VC = vital capacity.

Table 2. Covid-19 Related Clinical Outcomes in People Who Survived Hospitalization[a]

Characteristics	People With Covid-19		
	Total Cohort (n = 23)	General Ward Survivors (n = 16)	ICU Survivors (n = 7)
Covid-19 related clinical outcomes			
Initial pulmonary impairment measured from chest computed tomography, n (%)			
Normal	3 (13)	3 (19)	0 (0)
Minimal	4 (17)	4 (25)	0 (0)
Moderate	12 (52)	8 (50)	4 (57)
Extensive	4 (17)	1 (6)	3 (43)
Very extensive	0 (0)	0 (0)	0 (0)
Critical	0 (0)	0 (0)	0 (0)
Hospital length of stay *(d)*, median (IQR)	11 (6 to 16)	9 (5 to 13)	21 (14 to 46)
Active physical therapy *(no. of sessions)*, mean (SD)	6 (5)	5 (3)	9 (7)
Anticoagulant treatment, n (%)	9 (39)	3 (19)	6 (86)
ICU length of stay *(d)*, mean (SD)	6 (13)	0 (0)	21 (18)
Simplified Acute Physiology Score – II, mean (SD)	/	/	33 (17)
ARDS, n (%)	/	/	3 (43)
ECMO, n (%)	/	/	1 (14)
Invasive mechanical ventilation *(d)*, median (IQR)	/	/	0 (0 to 25)
Neuromuscular blockers *(d)*, median (IQR)	/	/	0 (0 to 11)
Amines *(d)*, mean (SD)	/	/	6 (0 to 19)

[a]Percentages may not sum to 100 due to rounding. Abbreviations: ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

Table 3. Cardiopulmonary Exercise Testing Performance at 6 Months in People With Covid-19 Who Survived Hospitalization[a]

Characteristics	People with Covid-19		
	Total Cohort	General Ward	ICU Survivors

	(n = 23)	Survivors (n = 16)	(n = 7)
Cardiopulmonary exercise testing			
Metabolic load			
Maximal workload *(W)*, mean (SD)	125 (54)	125 (51)	124 (65)
Maximal workload *(%)*, mean (SD)	90 (24)	91 (25)	87 (26)
VO2peak *(ml/min)*, mean (SD)	1642 (629)	1649 (635)	1628 (665)
VO2peak *(ml/kg/min)*, mean (SD)	19.0 (6.8)	19.8 (6.8)	17.2 (6.8)
VO2peak *(%)*, mean (SD)	84 (19)	87 (20)	77 (15)
People without a ventilatory threshold, n (%)	6 (26)	4 (25)	2 (29)
VO2vt/VO2predicted, mean (SD)	0.56 (0.08)	0.56 (0.09)	0.54 (0.04)
RER, mean (SD)	1.14 (0.15)	1.15 (0.17)	1.12 (0.09)
Watts/weight *(W/kg)*, mean (SD)	1.4 (0.6)	1.5 (0.6)	1.3 (0.7)
Lactates *(mmol/L)*, mean (SD)	5.4 (1.9)	5.8 (2.1)	4.6 (0.6)
VO2/watts *(ml/W/min)*, mean (SD)	10.7 (1.9)	10.8 (1.8)	10.4 (2.2)
Ventilatory pattern at VO2peak			
Vt *(L)*, mean (SD)	1.9 (0.6)	1.9 (0.7)	1.7 (0.5)
RR *(cpm)*, mean (SD)	35 (7)	33 (7)	38 (7)
VE *(L/min)*, mean (SD)	63 (21)	62 (20)	64 (25)
Breathing reserve *(%)*, mean (SD)	45 (13)	47 (14)	40 (11)
VE/VO2, median (IQR)	38 (30 to 43)	38 (30 to 42)	42 (31 to 43)
VE/VCO2, mean (SD)	33 (5)	33 (5)	34 (4)
VE/VCO2 slope, mean (SD)	32 (5)	32 (6)	34 (5)
Vd/Vt, median (IQR)	0.18 (0.08)	0.16 (0.08)	0.22 (0.10)
Cardiovascular adaptation at VO2peak			
Heart rate *(bpm)*, mean (SD)	143 (25)	148 (24)	132 (24)
Heart rate *(%)*, mean (SD)	85 (12)	87 (12)	81 (13)
VO2/HR *(ml/beat)*, mean (SD)	12 (4)	11 (4)	12 (4)
VO2/HR *(%)*, mean (SD)	100 (25)	101 (27)	97 (23)
Systolic arterial pressure *(mm Hg)*, mean (SD)	176 (32)	176 (34)	177 (31)
Diastolic arterial pressure *(mm Hg)*, mean (SD)	89 (9)	88 (9)	89 (8)
Arterial blood gas at VO2peak			
PaO2 *(kPa)*, mean (SD)	11.4 (2.2)	11.8 (1.8)	10.5 (2.9)
PaCO2 *(kPa)*, mean (SD)	4.8 (0.5)	4.8 (0.5)	5.0 (0.7)
pH, mean (SD)	7.38 (0.03)	7.38 (0.03)	7.38 (0.03)
Hb *(g/dl)*, mean (SD)	15 (2)	15 (2)	15 (1)
SaO2 *(%)*, median (IQR)	97 (95 to 98)	97 (95 to 98)	95 (89 to 98)
SpO2 *(%)*, median (IQR)	97 (96 to 98)	98 (96 to 99)	97 (91 to 98)
HCO3- *(mmol/L)*, mean (SD)	21 (2)	21 (2)	22 (3)
P(A-a)O2 *(kPa)*, mean (SD)	4.1 (2.2)	3.8 (1.9)	4.9 (3)
Perceived exertion at VO2peak			
Dyspnea (Borg scale), mean (SD)	5 (2)	5 (2)	6 (3)

| *Muscle fatigue (Borg scale),* mean (SD) | 5 (2) | 5 (2) | 5 (3) |

Table 4.   Univariate Relationship Between VO2peak (% Predicted Value) and Physiological Parameters[a]

| Physiological Parameter	VO2peak (%)	
	Rho	*p*
MIP *(cmH2O)*	0.376	.254
Watts/weight *(W/kg)*	0.781	< .001
VE/VO2	-0.149	.499
VE/VCO2	-0.318	.139
VE/VCO2 slope	-0.390	.066

[a]Pearson correlation test or logistic regression. Abbreviations: MIP = maximal inspiratory pressure; VCO2 = carbon dioxide production; VE = minute ventilation at VO2peak; VO2peak = pic oxygen uptake.

Figures legend
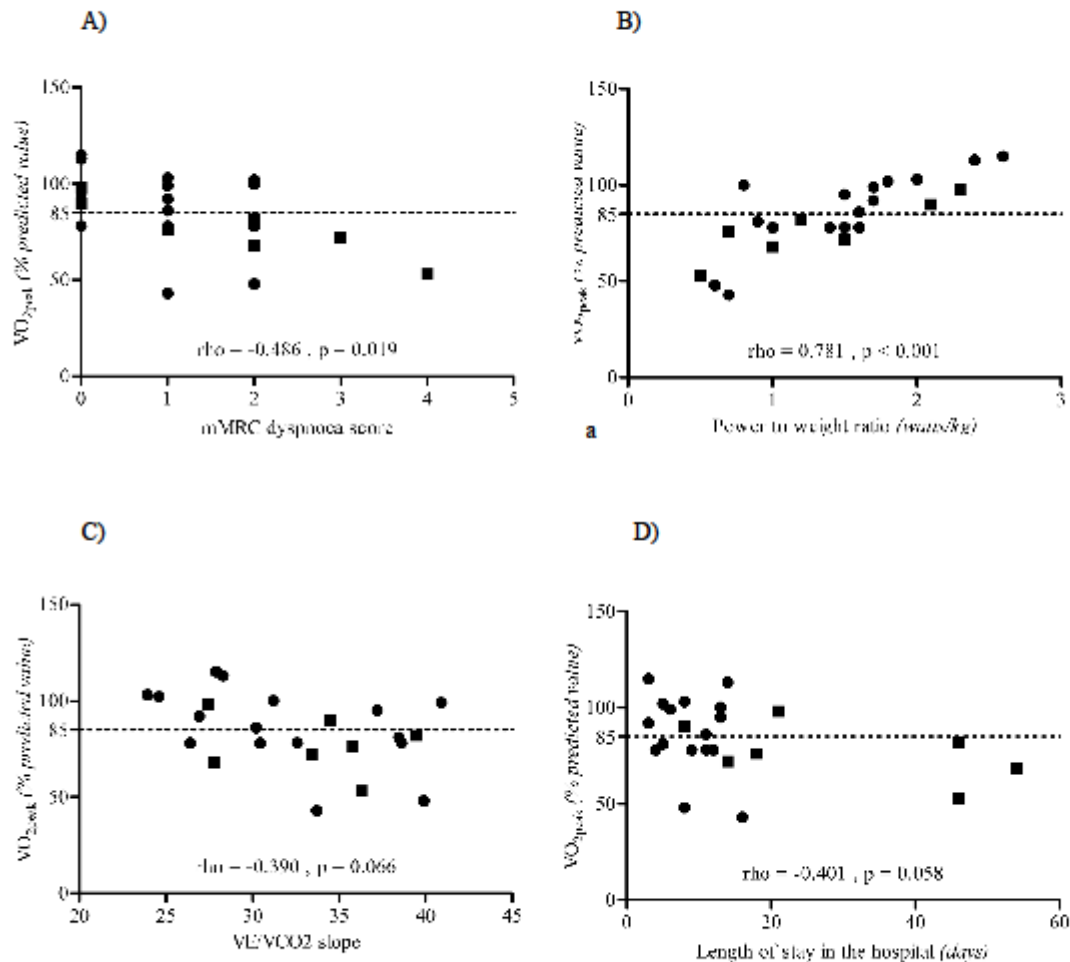
Figure 1: Relationship between VO2peak (% predicted value) and A) dyspnea 6 months following discharge from the hospital, B) power to weight ratio achieved during the CPET, C) slope of the ratio between minute ventilation relative to carbon dioxide production, D) length of stay in the hospital and E) the number of inpatient active physical therapist sessions during the hospitalization. Relationships were assessed using the Spearman rank order correlation test. mMRC = modified Medical Research Council dyspnea score, CPET = cardiopulmonary exercise testing, VE/VCO2 = slope of the ratio between minute ventilation relative to carbon dioxide production.
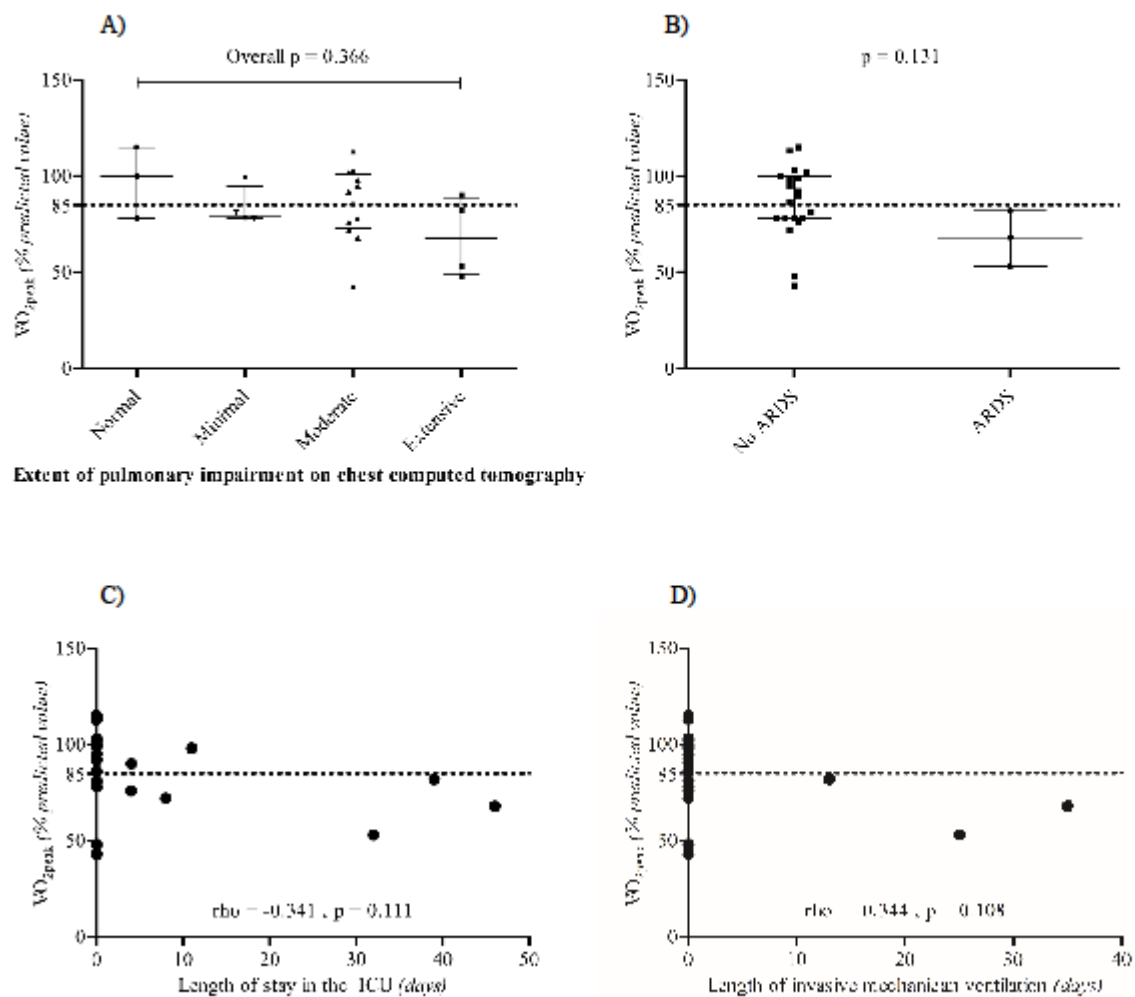
Figure 2: Relationship between VO2peak (% predicted value) and A) initial pulmonary impairment measured from chest computed tomography, B) the occurrence of an ARDS, C) the length of stay in ICU, D) the length of invasive mechanical ventilation, E) the duration of neuromuscular blockers administration and F) the duration of amines administration. The comparison of VO2peak (% theoretical value) between categorical data was assessed using the Kruskal-Wallis test (initial scan) and the Mann Whitney test (ARDS). Relationships were assessed using the Spearman rank order correlation test. ARDS = acute respiratory distress syndrome, ICU = intensive care unit.