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Guillaume Y Millet, Djahid Kennouche, Clément Foschia, Callum G Brownstein, Julien Gondin, Thomas Lapole, Diana Rimaud, Nicolas Royer, Guillaume Thiery, Vincent Gauthier, et al.

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**Cardiorespiratory fitness and neuromuscular function of mechanically ventilated intensive  
care unit Covid-19 patients**

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**Running title:** Cardiorespiratory and muscle function of intensive care unit Covid-19 patients

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## Abstract

**OBJECTIVES:** The aim of the present study was to investigate the level of cardiorespiratory fitness and neuromuscular function of intensive care unit (ICU) survivors after Covid-19 and to examine whether these outcomes are related to ICU stay/mechanical ventilation duration.

**DESIGN:** Prospective non-randomized study.

**SETTING:** Patients hospitalized in ICU for Covid-19 infection.

**PATIENTS:** 60 patients hospitalized in ICU (mean duration: 31.9±18.2 days) were recruited 4 to 8 weeks post-discharge from ICU.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Patients visited the laboratory on two separate occasions. The first visit was dedicated to quality of life questionnaire, cardiopulmonary exercise testing while measurements of the knee extensors neuromuscular function were performed in the second visit. Maximal oxygen uptake ( $\dot{V}O_{2max}$ ) was 18.3±4.5 mL·min<sup>-1</sup>·kg<sup>-1</sup>, representing 49±12% of predicted value, and was significantly correlated with ICU stay/mechanical ventilation (MV) duration ( $R=-0.337$  to  $-0.446$ ,  $P<0.01$  to  $0.001$ ), as were maximal voluntary contraction and electrically evoked peak twitch.  $\dot{V}O_{2max}$  (either predicted or in mL·min<sup>-1</sup>·kg<sup>-1</sup>) was also significantly correlated with key indices of pulmonary function such as predicted forced vital capacity or predicted forced expiratory volume in 1-s ( $R=0.430$  to  $0.465$ ,  $P \leq 0.001$ ) and neuromuscular function. Both cardiorespiratory fitness and neuromuscular function were correlated with self-reported physical functioning and general health status.

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**CONCLUSIONS:**  $\dot{V}O_2$ max was on average only slightly above the 18 mL·min<sup>-1</sup>·kg<sup>-1</sup>, i.e. the cut-off value known to induce difficulty in performing daily tasks. Overall, although low physical capacities at admission in ICU Covid-19 patients cannot be ruled out to explain the association between  $\dot{V}O_2$ max or neuromuscular function and ICU stay/MV duration, altered cardiorespiratory fitness and neuromuscular function observed in the present study may not be specific to Covid-19 disease but seem applicable to all ICU/MV patients of similar duration.

**KEYWORDS:** Covid-19, cardiorespiratory fitness, muscle, respiration artificial, intensive care unit, quality of life.

## Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 virus), primarily affects the respiratory system, although other organ systems are also involved (for details about the pathophysiology, see (1)). While the majority of people infected with Covid-19 will present no to mild-moderate symptoms, more severe disease is experienced by elderly populations and people with comorbidities. It has been estimated that around 30% of people infected with Covid-19 will require hospitalization and of those hospitalized, 20% will be admitted to an Intensive Care Unit (ICU) (2).

The negative effects of Covid-19 on the respiratory system, combined with the known effects of prolonged immobilization and mechanical ventilation (MV) on cardiorespiratory function, are likely to have severe implications for cardiorespiratory fitness (CRF). Assessment of CRF is most commonly performed through the measurement of maximal oxygen uptake ( $\dot{V}O_2\text{max}$ ), which measures the upper limit of  $O_2$  transport and utilization during exercise. Lower levels of aerobic capacity are associated with reduced independence during activities of daily living (3). For instance, it has been observed that individuals with a  $\dot{V}O_2\text{max}$  lower than  $18 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  report significant difficulty in performing daily tasks (4). Clinical cardiopulmonary exercise testing is the established clinical tool for assessing CRF in response to incremental exercise (5).

Physical function and fitness have been reported to be impaired following SARS-CoV infection (6). These functional limitations are important because people with SARS-CoV may experience residual impairments in physical function up to 1-2 years after the infection (2). Similarly, when considering patients with acute respiratory distress syndrome, 69% experienced declines in physical status (Medical Research Council score and/or 6-min walk

1 test) from their post-discharge state over a 5-year follow-up period (7). In Covid-19  
2 hospitalized patients tested 6 months post-infection, those who were more severely ill during  
3 their hospital stay had more severely impaired pulmonary diffusion capacities (8). However,  
4 in this study, only 4% of patients were admitted to ICU, and any potential effects of impaired  
5 pulmonary function on CRF was not assessed. Thus, objective physical function measures in  
6 Covid-19 patients admitted to ICU have yet to be thoroughly investigated.  
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16 In addition to CRF, lower muscle strength during early adulthood was associated with  
17 a higher risk of hospitalization, admission in ICU and mortality (9). These data, combined with  
18 the fact that ICU stay induces muscle deconditioning, particularly in ventilated patients (10)  
19 make the investigation of neuromuscular function in Covid-19 ICU survivors extremely  
20 relevant. Neuromuscular function encompasses both the central and the peripheral  
21 components. The central component (neural command) assesses the existence of a potential  
22 neural deficit, i.e. whether motor units are fully recruited. The peripheral component focuses  
23 on the muscle, independently of the neural drive. Maximal strength is the combination of the  
24 two components. To the best of our knowledge, such data do not exist in Covid-19 patients.  
25 The aim of this study was thus to thoroughly evaluate the level of CRF and lower limbs  
26 neuromuscular function in ICU survivors after Covid-19 and to better understand the etiology  
27 of both CRF (e.g. pulmonary/muscle causes) and neuromuscular function limitations.  
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## 51 **Methods**

### 52 **Patients and eligibility**

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54 The study cohort comprised 60 patients (8 women; age: 64.5±9.8 yr; height: 172.6±8.0 cm;  
55 body mass: 79.1±11.7 kg; body mass index (BMI): 26.5±3.7 kg·m<sup>-2</sup>) hospitalized in ICU for  
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1 Covid-19 infection recruited in 6 ICUs of University hospitals and private clinics in Saint-  
2 Etienne, Lyon and Grenoble (France) between May 2020 and August 2021. Time from  
3 discharge was  $51.7 \pm 15.4$  d, ICU stay duration was  $31.9 \pm 18.2$  d, days spent on MV was  
4  $22.8 \pm 14.9$  d and the sequential organ failure assessment score (SOFA) was  $5.7 \pm 2.7$ . This  
5 prospective non-randomized study was conducted according to the Declaration of Helsinki  
6 and received approval from a Committee on Human Research (n° 200405, Comité de  
7 Protection des Personnes 8 Ile de France - ClinicalTrials.org: NCT04363606). Written  
8 informed consent was obtained from all patients. Inclusion and exclusion criteria are  
9 presented in Figure 1.  
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23 Patients, for whom sequential organ failure assessment (SOFA) and simplified acute  
24 physiology score (SAPS 2) were assessed, visited the laboratory on two separate occasions to  
25 complete the protocol. Pre-ICU status was determined using Clinical Frailty Score, Charlson  
26 Comorbidity Index, and BMI at admission. The first visit was dedicated to questionnaires,  
27 cardiopulmonary exercise testing and familiarization to electrical stimulation and force  
28 measurements used in visit #2. The second visit, performed  $6.7 \pm 2.5$  days after visit #1, was  
29 dedicated to the neuromuscular function measurements. Out of the 60 patients, 10 were not  
30 allowed to participate to visit #2 or had adverse effects during the cardiopulmonary exercise  
31 testing performed in visit #1. The reasons are detailed in Supplemental Material. To avoid  
32 attrition bias, all subjects participating in the study were included in the statistical analysis. To  
33 minimize assessment bias, the same experimenter administered all the neuromuscular tests.  
34 The assessments were made blinded to the knowledge of ICU stay duration. To avoid selection  
35 bias, the study was proposed to all consecutive volunteers who met the inclusion criteria.  
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### *Health-related quality of life (visit #1)*

Health-related quality of life was assessed using the French version of the SF-36 questionnaire (11). A score between 0 and 100 is assigned to various domains, and aggregate into physical and mental components. The questionnaire includes assessments of bodily pain, general health, vitality, limitations in physical function, limitations in usual role activities due to physical problems, limitations in usual role activities due to emotional problems, limitations in social activities, and mental health.

### *Cardiopulmonary exercise testing (visit #1)*

Spirometric tests were completed in all patients to determine forced vital capacity, forced expiratory volume in one second, and maximum voluntary ventilation.

A maximal incremental cardiopulmonary exercise test using a cycle ergometer was conducted using a standard ramp-incremental protocol. Patients were seated on a standard bicycle ergometer with 12-lead electrocardiogram and gas exchange monitoring. Details of protocol and equipment are presented in Supplementary Material. Peripheral oxygen saturations ( $SpO_2$ ) and non-invasive blood pressure were monitored throughout the test. Desaturation during exercise was considered as significant when the difference in  $SpO_2$  from baseline was  $\geq 4\%$  (12).

The highest rolling 30-s average for  $\dot{V}O_2$ , minute ventilation ( $\dot{V}_E$ ) and respiratory exchange ratio were calculated.  $\dot{V}O_{2max}$  was expressed as absolute values ( $L \cdot min^{-1}$ ), and relative to body mass ( $mL \cdot min^{-1} \cdot kg^{-1}$ ). To describe the cardiorespiratory fitness of our sample, we also compared each participant's  $\dot{V}O_{2max}$  with reference values based on age and sex (i.e.

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$\dot{V}O_2$ max percent predicted values) (13). Ventilatory limitation to exercise was defined as previously suggested (12).

### *Quadriceps neuromuscular function (visit #2)*

Patients sat on an isometric dynamometer (ARS dynamometry; SP2, Ltd., Ljubljana, Slovenia). Details about the position and the equipment can be found elsewhere (14). After a standardized warm-up, patients performed the neuromuscular assessment. They first performed one maximal voluntary contraction with no stimulation. Subsequently, patients performed two maximal voluntary contractions (separated by 60 s) with single peripheral nerve stimulation delivered during the maximal voluntary contraction plateau followed by a single stimulation within 2 s of relaxation, for the calculation of maximal voluntary activation as an index of maximal central drive, as follows:

$$\text{Voluntary Activation} = \left[ \frac{1 - \text{superimposed Twitch}}{\text{Peak Twitch}} \right] \times 100$$

where peak twitch, also used as an index of muscle function, is the amplitude of the potentiated twitch. Maximal voluntary contraction torque was defined as the highest value. Peak twitch is expressed absolute values (in Nm) or relative to body mass ( $\text{Nm} \cdot \text{kg}^{-1}$ ).

### *Comparison with other cohorts*

To compare maximal voluntary contraction of our patients with healthy subjects, we used data from previous studies performed in our laboratory (n=77; age  $51.8 \pm 12.1$  yr; body mass  $77.1 \pm 16.2$  kg) and collected on the same isometric dynamometer. We also compared our

1 patients with a small cohort (n=33, age 50.3±12.8 yr; body mass 75.6±7.6 kg) of non-ICU Covid-  
2 19 patients.  
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### 8 *Statistical analysis*

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11 To assess the effects of ICU stay, MV duration and disease severity on CRF and  
12 neuromuscular function, Pearson's product moment correlations were performed against  
13 the objective variables of the study. Pearson's correlations were also used to test the  
14 relationships between indices of health-related quality of life and the objective variables and  
15 between  $\dot{V}O_2$ max and pulmonary and NM functions. An unpaired t-test was used to test the  
16 characteristics of patients with and without adverse events during the cardiopulmonary  
17 exercise testing. No imputation of missing values was performed. The alpha level was set at  
18 0.05. To compare our cohort with both healthy subjects (for maximal voluntary contraction)  
19 and Covid-19 patients who have not stayed in ICU (for CRF), a multiple linear regression to  
20 understand the effect of ICU stay, sex, age and body mass on different outcomes was used.  
21 All the possible interactions up to the 4<sup>th</sup> order were tested, using likelihood ratio test and a  
22 backward heuristic approach.  
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### 47 **Results**

48 Before admission, 42% of our patients were considered as obese (BMI>30 kg/m<sup>2</sup>). On average,  
49 patients had a Clinical Frailty Score of 2±1 and a Charlson Comorbidity Index of 2.9±1.5. There  
50 was no correlation between the pre-comorbid status (i.e. Charlson Comorbidity Index, Clinical  
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Frailty Score or Pre-BMI) and the ICU stay duration, MV duration, SOFA or SAPS2 scores.

Median and range of ICU stay duration was 29 days and [6-80 days], respectively.

The main parameters for lung function and at peak exercise during incremental cardiopulmonary exercise testing are presented in Tables 2 and 3, respectively. Most ventilatory and CRF outcomes were below the normative values. Fixing the values of all the other relevant explanatory variables (i.e. age, sex, body mass), forced vital capacity, forced expiratory volume in 1-s, and  $\dot{V}O_2\text{max}$  were significantly lower in ICU than non-ICU Covid-19 patients ( $P < 0.001$  to  $0.019$ ). No difference was found between the two groups for maximal voluntary ventilation.

The Charlson Comorbidity Index was negatively correlated with maximal voluntary contraction relative to body mass ( $R = -0.322$ ,  $P = 0.024$ ) but there were no correlations between the Charlson Comorbidity Index and relative ( $R = -0.117$ ,  $P = 0.392$ ) or absolute ( $R = -0.135$ ,  $P = 0.322$ )  $\dot{V}O_2\text{max}$ .

The percentage of patients put in prone positioning, receiving extracorporeal membrane oxygenation, neuromuscular blocking drugs and corticosteroids were 84%, 7%, 89% and 40%, respectively. There was a significant correlation ( $R = -0.303$ ;  $P = 0.031$ ) between  $W_{\text{max}}$  and the SOFA score but not with SAPS2. No other correlations were found between SOFA and any of the CRF or neuromuscular function variables measured in the present study.

ICU stay duration was significantly correlated with  $\dot{V}O_2\text{max}$  expressed in  $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  body mass ( $R = -0.446$ ,  $P < 0.001$ , Figure 2A) as well as with maximal voluntary contraction in both absolute ( $R = -0.504$ ,  $P < 0.001$ ) and relative to body mass ( $R = -0.449$ ,  $P = 0.001$ ) values and absolute peak twitch ( $R = -0.334$ ,  $P = 0.033$ ). Similarly, MV duration was significantly correlated with  $\dot{V}O_2\text{max}$  expressed in percent predicted values ( $R = -0.320$ ,  $P = 0.016$ ). MV duration was also

1 correlated with several indices of strength such as maximal voluntary contraction in absolute  
2 values ( $R=-0.429$ ,  $P=0.002$ ). Maximal voluntary contraction was significantly lower in Covid-19  
3 ICU survivors compared to healthy subjects ( $P<0.001$ ) [fixing the values of all the others  
4 relevant explanatory variables (i.e. ICU stay, age, sex and body mass)].  
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10 There were significant correlations between  $\dot{V}O_2\text{max}$  and indices of muscle strength,  
11 either expressed both in absolute values (i.e. in  $\text{L}\cdot\text{min}^{-1}$  and  $\text{Nm}$ :  $R=0.696$ ,  $P<0.001$ ) or in  
12 relative values (i.e.  $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  body mass and  $\text{Nm}\cdot\text{kg}^{-1}$  body mass:  $R=0.675$ ,  $P<0.001$ , Figure  
13 2B). Relative  $\dot{V}O_2\text{max}$  was also correlated to relative peak twitch ( $R=0.693$ ,  $P<0.001$ , Figure  
14 2C).  
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24 Forced vital capacity, forced expiratory volume in 1-s and maximum voluntary  
25 ventilation were  $83.7\pm 18.6\%$ ,  $89.4\pm 19.6\%$  and  $96.7\pm 20.2\%$  of predicted values. There were  
26 significant correlations between  $\dot{V}O_2\text{max}$  either in percent predicted values or in  $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$   
27  $\text{body mass}$  and indices of lung function, i.e. predicted forced vital capacity ( $R=0.491$ ,  $P<0.001$   
28 and  $R=0.430$ ,  $P=0.001$ ), predicted forced expiratory volume in 1-s ( $R=0.520$ ,  $P<0.001$  and  
29  $R=0.465$ ,  $P<0.001$ ) and maximum voluntary ventilation ( $R=0.440$ ,  $P<0.001$  and  $R=0.249$ ,  
30  $P=0.072$ ).  
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43 Significant desaturation during exercise from baseline levels was observed in 41.7% of the  
44 patients (mean desaturation  $\sim 5\%$ ). Minimum  $\text{SpO}_2$  during the cardiopulmonary exercise  
45 testing was significantly correlated with predicted forced vital capacity, and forced expiratory  
46 volume in 1-s ( $R=0.614$ ,  $R=0.579$ ,  $R=0.561$ , respectively; all  $P<0.001$ ). Based on the criteria  
47 defined by Benington et al. (12), 29% of the patients were classified as having pulmonary  
48 limitations to exercise. Removing these patients did not change  $\dot{V}O_2\text{max}$  ( $18.2\pm 4.4$   $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ).  
49 At  $\dot{V}O_2\text{max}$ , respiratory exchange ratio was  $1.14\pm 0.11$ . Three minutes after task failure,  
50 finger blood capillary lactatemia was found to be  $7.0\pm 2.0$   $\text{mmol/L}$ .  
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Finally, indices of health-related quality of life (see Table 3) were correlated with objective CRF and neuromuscular function outcomes. In particular,  $\dot{V}O_2\text{max}$  (relative to body mass) was correlated with PF, RP, and GH ( $R\leq 0.385-408$  and  $P<0.004$ ). Similarly, maximal voluntary contraction and peak twitch (relative to body mass) were correlated with RP and GH ( $R\leq 0.325-388$  and  $P<0.028$ ).

## Discussion

The present study aimed to investigate the cardiorespiratory and neuromuscular characteristics of ICU survivors after Covid-19 and to examine whether these outcomes were related to ICU stay/ventilation duration. The main results are that mean  $\dot{V}O_2\text{max}$  was (i) slightly above the  $18\text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  cut-off value known to induce difficulty in performing daily tasks (e.g. climbing stairs will require an aerobic capacity close to this value, i.e. 5 METS), (ii) negatively correlated to ICU stay/MV duration, (iii) correlated with key indices of pulmonary and neuromuscular functions and (iv) associated with limitations in self-reported physical function. The present results also showed that muscle strength and quality of life was deteriorated when compared to a healthy control population.

### *$\dot{V}O_2\text{max}$ : effects of Covid-19 vs ICU stay*

In the present study,  $\dot{V}O_2\text{max}$  was directly assessed 4 to 8 weeks post-ICU and was found to be very low, i.e.  $18.3\text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$  or 49% of predicted values. Braga et al. (2022) assessed CRF a median of 25 days after discharge in hospitalized Covid-19 patients and reported a  $\dot{V}O_2\text{peak}$  of  $18.7\text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ . This is similar to the present study, despite their patients being

1 less severely ill, since not all (58%) were admitted in ICU and only 18% needed invasive MV,  
2 probably because their patients were tested following a shorter time lapse after discharge (25  
3 days vs 52 days post-discharge in the present study). Our data are also similar to another study  
4 with a smaller cohort showing that Covid-19 ICU patients had 57% of predicted values (15)  
5 compared to 49% in the present study. In our own comparison with non-ICU Covid-19 patients,  
6 we found that, when normalizing to other relevant explanatory variables (i.e. age, sex, body  
7 mass),  $\dot{V}O_2\text{max}$  was significantly higher in non-ICU than in ICU Covid-19 patients. It has also  
8 been reported that non-Covid-19 ICU survivors tested  $24 \pm 14$  days after hospital discharge had  
9  $\dot{V}O_2\text{max}$  of  $13.8 \text{ mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$  (12). Since ICU stay or MV duration were comparable in the two  
10 cohorts, the higher values in ICU Covid-19 patients of the present study could be due to the  
11 fact that our patients were tested following a longer time lapse after discharge. ICU Covid-19  
12 patients may have had low  $\dot{V}O_2\text{max}$  before going to the hospital (16). However (i) the Clinical  
13 Frailty Score ( $2 \pm 1$ ) and Charlson Comorbidity Index ( $2.9 \pm 1.5$ ) show that the patients were  
14 not fragile and did not have major comorbidities at admission and (ii) the Charlson  
15 Comorbidity Index was not correlated to  $\dot{V}O_2\text{max}$ . Overall, this suggests that the deteriorated  
16 CRF is not specific to ICU Covid-19 patients (despite their ventilatory limitations, see below)  
17 but is applicable to all ICU/MV patients.

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Three quarter of the patients hospitalized due to Covid-19 (not only ICU patients) have been shown to have persistent pulmonary symptoms, in particular breathlessness (17).  $\dot{V}O_2\text{max}$  was significantly correlated with predicted forced vital capacity and forced expiratory volume in 1-s in the present study. Altogether the present results may suggest that the pulmonary limitations are significant during exercise in patients with severe forms of Covid-19. However, we speculate that this correlation was related to the effects of ICU stay/MV duration on both  $\dot{V}O_2\text{max}$  and spirometry parameters rather than to the effects of Covid-19



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*per se*. Only one patient demonstrated significant desaturation during exercise from baseline levels (> 4%) in Benington et al. (12) compared to 42% in the present study and 23% in Skjorten et al. (18). However, removing the patients with pulmonary limitations in the present study did not change  $\dot{V}O_2\text{max}$  so that they cannot fully explain the low CRF of our patients, as previously suggested in SARS patients (19).

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Importantly,  $\dot{V}O_2\text{max}$  was also associated with self-reported limitations in physical function as well as limitations in usual activities due to physical problems in the present experiment (two items of the SF-36 questionnaire). This is in line with data showing that lower levels of aerobic capacity are associated with deteriorated functional independence during activities of daily living (2). Glimelius Petersson et al. (20) reported mental and physical components of the SF-36 collected two months after (non-Covid-19 patients) ICU discharge of  $43\pm 29$  and  $32\pm 24$ , respectively, that is in line with our findings of  $42\pm 17$  and  $43\pm 16$ . In contrast, when comparing our data with normative values for a similar age (21), it is clear that our patients are below those of healthy subjects.

### *Neuromuscular function*

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Maximal voluntary contraction, i.e. the combination of both central drive (assessed by maximal voluntary activation) and muscle function (assessed by peak twitch), was significantly lower in Covid-19 ICU survivors compared to healthy subject.  $\dot{V}O_2\text{max}$  correlated with muscle (i.e. peripheral component) strength, including when both  $\dot{V}O_2\text{max}$  and peak twitch were normalized to body mass. One possibility is that muscle limitations may have contributed to impaired CRF. Alternatively, it could be argued that the physical function (including both

1  
2 maximal strength and CRF) was negatively impacted by ICU duration or that people with a  
3 higher  $\dot{V}O_2\text{max}$  were more active, and as a result had greater muscle strength.  
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6 Importantly, ICU acquired weakness has been reported as a major symptom in ICU  
7 patients (22, 23). For example, over one quarter of patients develops significant muscle  
8 wasting (10) and weakness (24) during ICU stay, particularly in the lower limb muscle groups.  
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10 ICU acquired weakness was reported to be 27% at hospital discharge post-ICU due to Covid-  
11 19 (25). The present study did not allow to ascertain the existence of ICU acquired weakness  
12 since no Medical Research Council scores were performed and it has been shown that muscle  
13 strength was associated with the risk of Covid-19 hospitalization (9, 26) so that the patients  
14 may have been weak before admission. Yet, it is worth reporting that significant correlations  
15 were found in the present study between indices of muscle function and self-reported  
16 limitations in physical function as well as limitations in usual role activities due to physical  
17 problems. Maximal voluntary activation ( $87\pm 8\%$ ) was found to be in normal range of values  
18 for healthy population (e.g.  $87\pm 9\%$  in endurance-trained athletes, (27)). Still, voluntary  
19 activation was correlated with self-reported limitations in usual role activities due to physical  
20 problems. Both  $\dot{V}O_2\text{max}$  and indices of neuromuscular function were thus correlated with the  
21 general health status and limitations in usual role activities due to physical problems in the  
22 present study. Altogether, the neuromuscular function data presented in the present study  
23 reinforce the need for tailored rehabilitation in this population, as recently suggested (25, 28,  
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56 *Effects of ICU stay and MV duration*  
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In the present study, significant correlations were found between the length of the ICU stay and  $\dot{V}O_2\text{max}$ . There are two possible explanations for this finding. Firstly, a negative relationship between  $\dot{V}O_2\text{max}$  and hospitalization following Covid-19 infection has previously been demonstrated (16). Accordingly, it is possible that patients with a lower  $\dot{V}O_2\text{max}$  prior to Covid-19 infection had a greater risk of more severe symptoms, and thus a longer ICU stay. Conversely, given that inactivity is associated with reductions in  $\dot{V}O_2\text{max}$  in a dose-response manner (30), the more prolonged ICU stay would be expected to induce more severe deconditioning and reductions in  $\dot{V}O_2\text{max}$ . This could be partly due to longer usage of sedative medications and neuromuscular blockades. Regardless of the cause, these results highlight the necessity of also providing structured aerobic training interventions in ICU Covid-19 patients. Based on the association between  $\dot{V}O_2\text{max}$  and ICU stay, we suggest that this is particularly important for people who have stayed more than 32 days in ICU. Those data agree with a recent paper arguing that cardiopulmonary exercise testing shows great promise in the guidance of rehabilitation in functionally limited ICU survivors (31).

The same reasoning as above applies to neuromuscular function. Indeed, as mentioned above, muscle strength has been found to be associated with the risk of Covid-19 hospitalization (26) and immobility induces muscle deconditioning (23). Significant correlations were found in the present study between maximal strength/peak twitch and ICU stay/MV duration. This is in line with a previous study showing that patients with ICU acquired weakness post-Covid-19 had longer ICU stays than their non-ICU acquired weakness counterparts (30 vs 19 days) (25). It has also been suggested that the rate of limb muscle weakness found in Covid-19 ICU patients was higher than in non-Covid-19 ICU patients, potentially due to the longer MV duration (32). We also found a strong correlation between  $\dot{V}O_2\text{max}$  and maximal voluntary contraction (both absolute et relative to body mass) and peak

1 twitch (an index of muscle function), both variables being correlated with ICU stay and MV  
2 durations as discussed above. This suggests that resistance training may also be beneficial to  
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5  $\dot{V}O_2\text{max}$  in these patients.  
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### 10 11 *Limitations*

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14 We cannot exclude the possibility that the ICU Covid-19 survivors who made themselves  
15 available for testing were not representative of all the survivors (12) or, on the contrary, that  
16 some fragile patients (e.g. with neuromyopathy) were not able to be recruited for the present  
17 study, so some degree of bias could have thus been present. It is also unclear whether the  
18 findings from the present study are generalizable to all Covid-19 patients from different  
19 demographic and cultural backgrounds, or for all variants. Cardiopulmonary exercise testing  
20 was performed with testing filters that have an inherent resistance to flow which in most  
21 circumstances are unlikely to limit ventilation and impact exercise performance (5). Despite  
22 that these filters are not recommended when performing cardiopulmonary exercise testing,  
23 they were used for safety reasons (33).  
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### 44 **Conclusion**

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48 Cardiorespiratory fitness of Covid-19 patients after 32 days in ICU was extremely low as shown  
49 by the mean  $\dot{V}O_2\text{max}$  being less than 50% of predicted values and just above the cut-off value  
50 known to induce difficulty in performing daily tasks. This low  $\dot{V}O_2\text{max}$  was associated with self-  
51 reported limitations in physical function and general health status. Other important findings  
52 of the present study are that key indices of pulmonary and neuromuscular functions were  
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1 associated with  $\dot{V}O_2$ max and that were both correlated with ICU stay and mechanical  
2 ventilation duration. These data emphasize the need for tailored (aerobic or resistance or  
3 combined training) rehabilitation programs for severe Covid-19 patients, particularly those  
4 who have stays at ICU over a month. However, these findings may not be specific for Covid-  
5 19 patients but be applicable to all ICU/mechanically ventilated patients for a similar duration.  
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### 17 **Acknowledgements**

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21 their help in collecting the data.  
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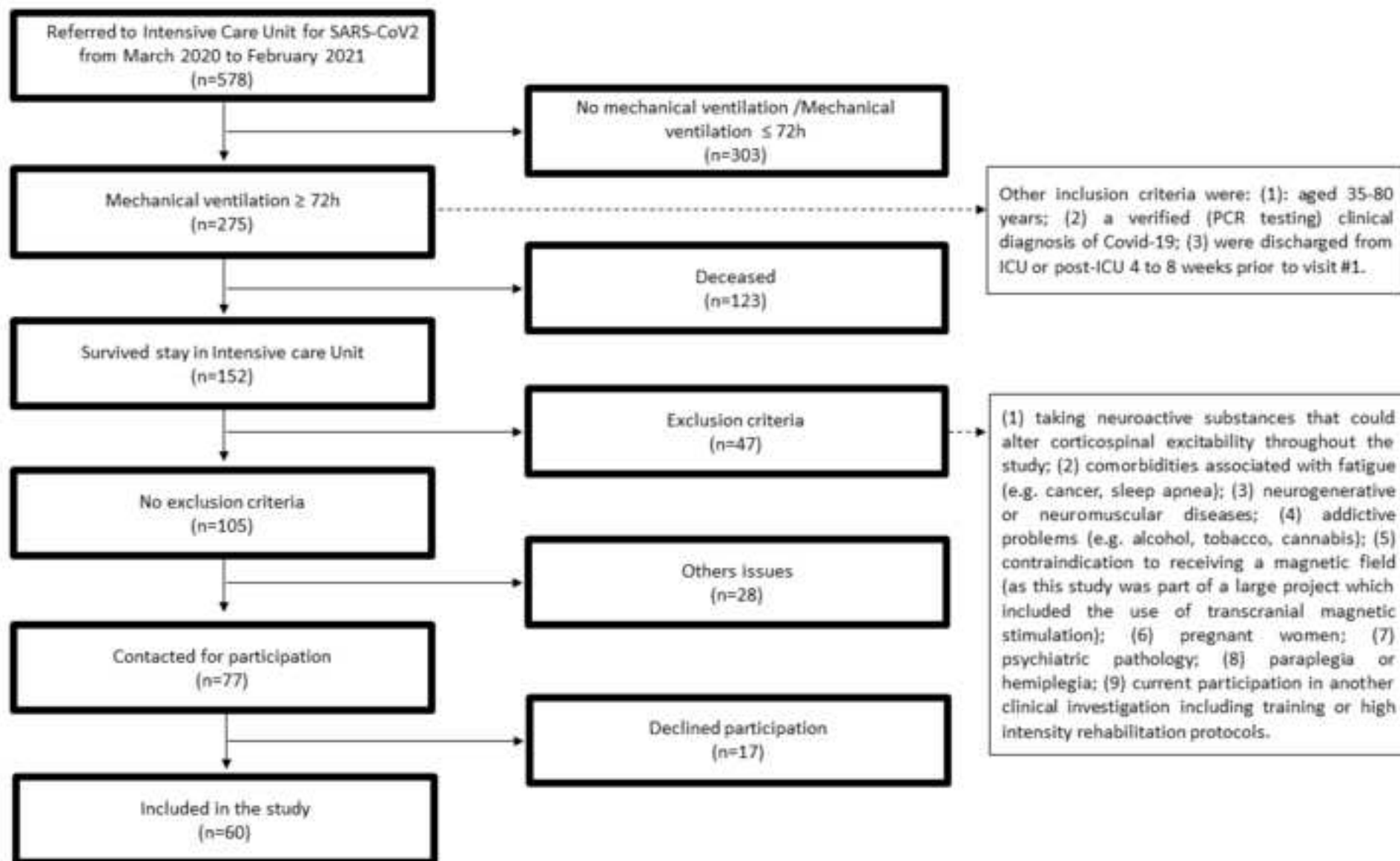
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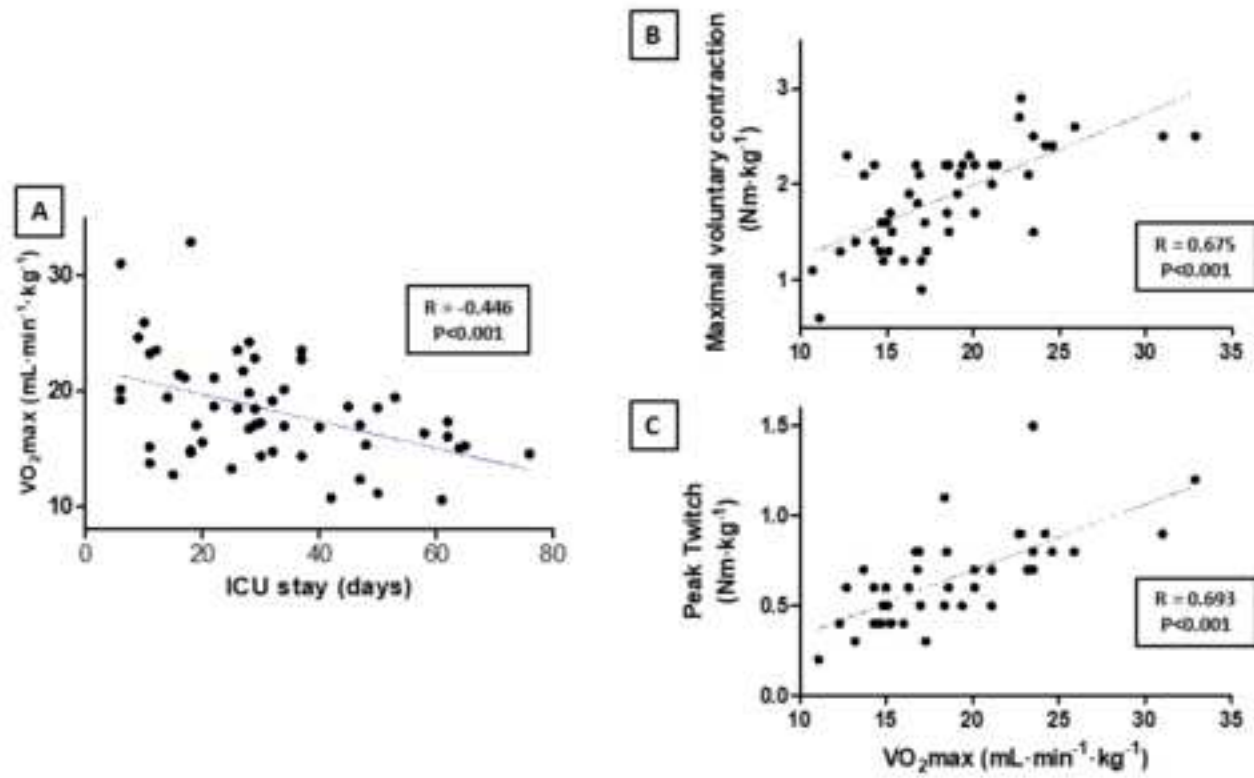


## Figures Legends

**Fig. 1.** Flowchart of the study.

**Fig. 2.** Relationship between ICU stay duration and  $\dot{V}O_2\text{max}$  (panel A, n=56), between  $\dot{V}O_2\text{max}$  and maximal voluntary contraction (panel B, n=49) and between  $\dot{V}O_2\text{max}$  and peak twitch (panel C, n=41). All parameters are expressed relative to body mass.





**Table 1.** Characteristics of patients without and with adverse events during the clinical cardiopulmonary exercise testing.

<b>Characteristic</b>	<b>Non-adverse events (n=50)</b>	<b>Adverse events (n=10)</b>	<b>All (n = 60)</b>
Age (y)	63.5 ± 9.9	69.5 ± 8.0	64.5 ± 9.8
Females (%)	12%	20%	14%
Height (cm)	172.3 ± 7.5	173.7 ± 10.5	172.6 ± 8.0
Body mass at admission (kg)	87.2 ± 12.6	84.8 ± 14.4	86.8 ± 12.8
BMI at admission (kg·m <sup>-2</sup> )	29.5 ± 4.2	27.7 ± 4.1	29.2 ± 4.2
Body mass at visit #1 (kg)	79.4 ± 11.6	78.1 ± 13.1	79.1 ± 11.7
BMI at visit #1 (kg·m <sup>-2</sup> )	26.8 ± 3.7	25.5 ± 3.8	26.5 ± 3.7
TFD (d)	51.3 ± 15.6	54.0 ± 15.1	51.7 ± 15.4
ICU stay duration (d)	30.0 ± 16.5	43.7 ± 23.1	31.9 ± 18.2
Days spent on MV (d)	21.9 ± 15.2	29.7 ± 13.9	22.8 ± 14.9
SOFA Score	5.8 ± 2.8	5.2 ± 2.3	5.7 ± 2.7
SAPS II	37.4 ± 12.0	43.2 ± 17.1	38.3 ± 13.0
Charlson Comorbidity Index	2.8 ± 1.5	3.6 ± 1.3	2.9 ± 1.5

*BMI*: body mass index, *TFD*: time from discharge, i.e. delay between ICU discharge and inclusion visit; *MV*: mechanical ventilation. *SOFA*: sequential organ failure assessment; *SAPS II*: simplified acute physiology score.

**Table 2.** Selected parameters of lung function at rest (all n = 57, except slow vital capacity: n = 39).

	Mean $\pm$ SD	Range
FVC (L)	3.22 $\pm$ 0.31	1.33-4.83
FVC (% pred. values)	83.7 $\pm$ 18.6	41-123
FEV1 (L)	2.68 $\pm$ 0.75	1.23-4.06
FEV1 (% pred. values)	89.4 $\pm$ 19.6	38-136
MVV (L·min <sup>-1</sup> )	109.6 $\pm$ 31.6	49.3-186.0
MVV (% pred. values)	96.7 $\pm$ 20.2	50-146

*FVC*: forced vital capacity; *FEV1*: forced expiratory volume in one second, *MVV*: maximum voluntary ventilation.

**Table 3.** Selected parameters at peak exercise during incremental cardiopulmonary exercise and main parameters of the neuromuscular function, blood parameters and quality of life.

	Mean $\pm$ SD	Range
<b>Cardiopulmonary exercise testing</b> (all n=56, except lactatemia: n = 40)		
$\dot{V}O_2$ max (L·min <sup>-1</sup> )	1.446 $\pm$ 0.4	0.813-2.860
$\dot{V}O_2$ max (mL·min <sup>-1</sup> ·kg <sup>-1</sup> )	18.3 $\pm$ 4.5	10.5-32.9
$\dot{V}O_2$ max (% pred. values)	49 $\pm$ 12%	27%-80%
Wmax (W)	97 $\pm$ 32	30-190
Wmax (W·kg <sup>-1</sup> )	1.24 $\pm$ 0.41	0.40-2.33
$\dot{V}_E$ max (L·min <sup>-1</sup> )	74.9 $\pm$ 20.2	41.0-126.5
Breathing reserve (L·min <sup>-1</sup> )	35 $\pm$ 26	-23-106
SpO <sub>2</sub> at rest (%)	98.5 $\pm$ 1.9	91.0-100.0
SpO <sub>2</sub> min (%)	93.7 $\pm$ 5.5	80.0-100.0
RER	1.14 $\pm$ 0.11	0.92-1.52
Lactatemia 3 min post-exh (mmol·L <sup>-1</sup> )	7.0 $\pm$ 2.0	4.0-12.6
<b>Neuromuscular function</b>		
MVC (Nm) (n = 49)	150.3 $\pm$ 41.8	75.8-244.6
MVC (Nm·kg <sup>-1</sup> )	1.91 $\pm$ 0.49	0.95-2.89
PTw (Nm) (n = 41)	51.9 $\pm$ 21.3	21.5-121.5
PTw (Nm·kg <sup>-1</sup> )	0.66 $\pm$ 0.26	0.27-1.55
VA (n = 39)	87 $\pm$ 8%	59%-99%
<b>Quality of life (SF-36)</b> (n = 57)		
Physical component	43 $\pm$ 16	13 - 82
Mental component	42 $\pm$ 17	18 - 82
Physical functioning	59 $\pm$ 24	0 – 100
Limitations due to physical problems	17 $\pm$ 31	0 – 100
Limitations due to emotional problems	26 $\pm$ 39	0 – 100
Vitality	44 $\pm$ 20	6 – 94
Mental health	41 $\pm$ 13	15 – 70
Social functioning	58 $\pm$ 21	13 – 100
Bodily pain	42 $\pm$ 28	0 – 100
General health	56 $\pm$ 14	30 – 90

$\dot{V}O_2$ max: maximal oxygen uptake, *Pred*: predicted, *Wmax*: maximal aerobic power,  $\dot{V}_E$ max: maximal ventilation, *SpO<sub>2</sub>*: arterial saturation in oxygen, *RER*: respiratory exchange ratio, *exh*: exhaustion, *MVC*: maximal voluntary contraction, *PTw*: peak twitch, *VA*: maximal voluntary activation.



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