ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Exercise intolerance in post-COVID19 survivors after hospitalization

Mariana L Lafetá, Vitor C Souza, Thaís C F Menezes, Carlos G Y Verrastro, Frederico J Mancuso, André Luis P Albuquerque, Suzana E Tanni, Meyer Izbicki, Júlio P Carlstron, Luiz Eduardo Nery, Rudolf K F Oliveira, Priscila A Sperandio, Eloara V M Ferreira

Please cite this article as: Lafetá ML, Souza VC, Menezes TCF, *et al*. Exercise intolerance in post-COVID19 survivors after hospitalization. *ERJ Open Res* 2023; in press (https://doi.org/10.1183/23120541.00538-2022).

Exercise intolerance in post-COVID19 survivors after hospitalization

Mariana L Lafetá [1], Vitor C Souza[1], Thaís C F Menezes[1], Carlos G Y Verrastro[5], Frederico J Mancuso[2], André Luis P Albuquerque[4], Suzana E Tanni[3], Meyer Izbicki[1], Júlio P Carlstron[1], Luiz Eduardo Nery[1], Rudolf K F Oliveira[1], Priscila A Sperandio[1], Eloara V M Ferreira[1]

[1] Pulmonary Function and Clinical Exercise Physiology Unit (SEFICE), Division of Respiratory Diseases, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

[2] Division of Cardiology, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

[3] Division of Internal Medicine of Botucatu Medical School, São Paulo State University-UNESP, Botucatu, Brazil.

[4] Pulmonary Division, Heart Institute (INCOR), Clinical Hospital HCFMUSP, Faculty of the Medicine University of Sao Paulo, Sao Paulo, Brazil; Sírio-Libanês Teaching and Research Institute, São Paulo, Brazil

[5] Radiology Division, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

Corresponding author: Eloara V M Ferreira, E-mail: eloara.ferreira@unifesp.br, Tel: +55 11 55764848

Author's contribution:

Responsible for the data analysis and content of the article: M.L.L, S.E.T, R.K.F.O and E.V.M.F.

Responsible for drafting the work: M.L.L, A.L.P.A, S.E.T. and E.V.M.F.

Responsible for data collection: M.L.L, V.C.S, T.C.F.M, P.A.S, J.P.C. and E.V.M.F.

Responsible for the image analysis: C.G.Y.V, M.I., F.J.M and E.V.M.F.

Revising critically for important intellectual content: L.E.N., A.L.P.A, P.A.S, R.F.K.O. and E.V.M.F

Final approval of the content of the manuscript: M.L.L., A.L.P.A, L.E.N, P.A.S, R.K.F.O and E.V.M.F

Go to home: Post-COVID19 survivors may have exercise intolerance, in our study this was related to high VD/VT at exercise and decreased FVC%pred, suggesting pulmonary microcirculatory injury and ventilatory impairment influence aerobic capacity.

Word count: 3104.

ABSTRACT

Rationale: Post-COVID19 survivors frequently have dyspnea that can lead to exercise intolerance and lower quality of life. Despite recent advances, the pathophysiological mechanisms of exercise intolerance in the post-COVID19 patients remain incompletely characterized. **Objectives:** To clarify the mechanisms of exercise intolerance in post-COVID19 survivors after hospitalization. **Methods:** Prospective study evaluated consecutive patients previously hospitalized due to moderate-to-severe/critical COVID19. Within 90±10 days (mean±SD) of COVID19 acute symptoms onset, patients underwent a comprehensive cardiopulmonary assessment, including a cardiopulmonary exercise testing with earlobe arterialized capillary blood gas analysis. **Measurements and Main Results:** Eighty-seven patients were evaluated, their mean±SD peak oxygen consumption were 19.5±5.0ml/kg/min, and the tertiles were: ≤17.0, 17.1-22.2 and ≥22.3ml/kg/min. Hospitalization severity was similar among the three groups; however, at the follow-up visit, they reported a greater sensation of dyspnea, along with indices of impaired pulmonary function, and abnormal ventilatory, gas-exchange and metabolic responses during exercise compared to patients with peak oxygen consumption >17ml/kg/min. By multivariate logistic regression analysis (ROC curve analysis) adjusted for age, sex and pulmonary embolism, a peak dead space fraction of tidal volume ≥29 and a resting forced vital capacity ≤80%predicted were independent predictors of reduced peak oxygen consumption. **Conclusions:** Exercise intolerance in the post-COVID19 survivors was related to a high dead space fraction of tidal volume at peak exercise and a decreased resting forced vital capacity, suggesting that both pulmonary microcirculation injury and ventilatory impairment could influence aerobic capacity in this patient population. **Keywords:** cardiopulmonary exercise testing, exercise capacity, dead space, post-COVID19 syndrome, dyspnea**.**

Word count: 236.

INTRODUCTION

In March 2020, COVID19 was characterized by the World Health Organization as a pandemic infection and has been considered an international public health emergency for the past two years. A few months after the pandemic's start, Brazil had the second highest number of confirmed COVID19 cases worldwide. In April 2021, Brazil had become the epicenter of the COVID19 pandemic, with over 4.000 deaths per day [1].

COVID19 infection may be asymptomatic in the acute phase, but clinical presentation might also range from mild respiratory symptoms to severe respiratory failure with associated acute respiratory distress syndrome (ARDS). Additionally, clinical presentation might include extrapulmonary symptoms [2]. After hospitalization, patients may remain symptomatic and this could be related to cardiac/lung sequalae's and/or post-COVID19 syndrome [3].

The post-COVID19 syndrome is defined by the presence of persistent symptoms 12 weeks after the onset of COVID19 and is not attributable to other known causes [3]. Among the most frequent signs and symptoms reported in post-COVID19 syndrome are fatigue, muscle weakness, dyspnea, hypoxemia, depression, anxiety, sleep and cognitive disorders, along with exercise intolerance [3–5], the latter of which might lead to a significant decrease in functional capacity and quality of life. Different hypotheses for mechanisms of exercise intolerance after COVID19 infection have been explored so far, and physical deconditioning has been described as one of the most likely driving forces of patient's symptoms [6, 7], despite COVID19 complexity and potential for multiorgan involvement.

In this context, recent findings suggest that exercise limitation in post-COVID19 survivors in more severe patients may be related to: i) central cardiocirculatory disorder due to chronic myocardial inflammation and/or pulmonary microvascular injury [8] for example; ii) ventilatory inefficiency [9, 10] due to increased dead space as a fraction of tidal volume (VD/VT), possibly

related to endothelial and/or microvascular dysfunction [11]; iii) reduced peripheral muscle oxygen extraction [11, 12]. In mild patients post-COVID19 syndrome, dysfunctional breathing was a relevant mechanism of exercise intolerance [12]. Nevertheless, despite these recent advances, the pathophysiological mechanisms of exercise intolerance in the post-COVID19 survivors remain incompletely characterized. In the current study, we aimed to clarify the mechanisms of exercise intolerance associated with reduced aerobic capacity after moderate-to-severe/critical COVID19 hospitalization.

MATERIALS AND METHODS

Study design and participants

The current study is part of an observational prospective Brazilian initiative to evaluate clinical symptoms, respiratory, radiological and metabolomic function in patients who were hospitalized due to COVID19 (The FENIX Study, Brazilian Clinical Trials Registry ReBEC: RBR-8j9kqy).

The current report presents data from consecutive adult patients from the post-COVID19 Outpatient Clinic of the Federal University of São Paulo (Unifesp). All included patients had the first medical visit after hospital discharge between August 2020 and May 2021 and had the following characteristics at the time of COVID19 hospitalization (inclusion criteria): i) confirmed diagnosis of COVID19 by reverse transcription polymerase chain reaction (RT-PCR); ii) received supplemental oxygen (O_2) support and iii) had acute lung parenchymal involvement confirmed by chest computed tomography (CT) scan.

Patients were invited to participate in the study in their first clinical outpatient evaluation after hospital discharge. Those patients who fulfilled the study inclusion criteria and signed an informed consent form had their clinical information recorded and within 90±10 days after the

onset of COVID19 acute symptoms, performed a comprehensive cardiopulmonary assessment, including a cardiopulmonary exercise testing (CPET) with earlobe arterialized capillary blood gas analysis. All other tests, pulmonary lung function, echocardiogram and high-resolution chest CT (HRCT), were performed within ten days from CPET (Figure 1).

Patients in palliative cancer care, with psychiatric disturbances, musculoskeletal impairment to perform the exercise, and uncontrolled known cardiovascular, endocrine-metabolic, or renal diseases were excluded from the study. Patients who could not complete the study follow-up visit were also excluded (Figure E1 – online data supplement).

The methodological description of pulmonary function test and modified Medical Council Research (mMRC) are described and included in the online supplement [13–15].

Cardiopulmonary Exercise Testing (CPET)

Patients performed a symptom-limited, ramp-incremental cycle ergometer CPET using a computer-based exercise system with breath-by-breath analysis of metabolic, ventilatory and cardiovascular variables (ULTIMA CardioO_2, Med Graphics, Saint Paul, MN, USA). The work rate was individually selected to provide an incremental phase of 7-12 min (5 to 20 W/min) and started after a 2 min unloading warm-up period. The measures obtained was described elsewhere [16] and included on online supplement. Earlobe arterialized capillary blood gas samples (Heparinated 200-I microtubes, radiometer, Copenhagen, Denmark), were drawn at rest and at peak exercise after applying vasodilator capsaicin cream (Moment® 0.075%, Apsen Pharmaceutical, São Paulo, Brazil). The blood analyses were immediately performed (ABL800, Radiometer®, Brønshøj, Denmark) to obtain lactate and gas exchange variables (PaO_2, $PaCO_2$ and SaO_2). Measures of alveolar-arterial O_2 gradient ($P(A\text{-}a)O_2$), arterial end-expiratory CO_2 gradient ($P(a\text{-}ET)CO_2$) and VD/VT (Enghoff modification of the Bohr equation) were then calculated [16].

Data analysis

In the study design, there were not enough studies for sample calculation, for this sample, the confidence interval was used for a population proportion (95% CI) considering a third of the patients with reduced $_{PEAK}V'O_2$. Descriptive statistics are present as mean and standard deviation median and interquartile range of frequencies. Patients were categorized according to $_{PEAK}V'O_2$ tertiles: ≤17.0ml/kg/min, 17.1-22.2ml/kg/min or ≥22.3ml/kg/min. Comparisons between more than two groups were performed with One-way ANOVA with Bonferroni or Kruskal-Wallis post-hoc analysis, according to the data distribution. Correlation analyses were performed using Pearson's or Spearman's coefficients to identify variables significantly associated with $_{PEAK}V'O_2$ml/kg/min. Receiver operating characteristic (ROC) curves were drawn for variables that had a high correlation with $_{PEAK}V'O_2$ while accounting for the presence or absence of a $_{PEAK}V'O_2$≤17.0ml/kg/min. The thresholds for each ROC curve were obtained from the points with the greatest sum of sensitivity and specificity. After dichotomizing the variables of interest according to ROC thresholds, univariate logistic regression was performed to explore potential $_{PEAK}V'O_2$≤17.0ml/kg/min predictors. Non-collinear variables, (r ≥0.6) from the univariate analysis from different pathophysiological domains (i.e., symptoms, lung function, ventilatory, gas-exchange or metabolic responses to exercise) were included in multivariate logistic regression models adjusted for age, sex and pulmonary embolism to estimate the probability of having a $_{PEAK}V'O_2$≤17.0ml/kg/min, a second model was analyzed with adjustment for age, sex and the presence of any comorbidity (Table E4 – online data supplement). The accepted statistical significance value was <0.050. Graphs were performed with GraphPad Prism (version 9.3.0 for Windows, GraphPad Software), and statistical analyses were performed using SPSS™ for Windows, version 21.0 (Armonk, NY: IBM™ Corp).

RESULTS

Ninety-six patients were eligible to participate in this study. Nine patients were excluded. Patient exclusion occurred due to acute arthritis (n=01), severe thrombocytopenia (n=01), acute deep vein thrombosis (n=01), uncontrolled systemic arterial hypertension (n=01), acute metabolic acidosis (n=01) and inability to perform the study follow-up visit (n=04). Therefore, the study sample was composed of eighty-seven patients.

Of the 87 included patients, 54% were admitted to the ICU and 49% had ≥50% of ground-glass opacities on chest CT scan. The mean age was 53±13 years-old, 62% were male, and 63% had ≥2 comorbidities (Table 1). Systemic hypertension, previous smoking history, and obesity were the most common comorbidities among studied patients (Table E1-online data supplement). Detailed information regarding the patient's comorbidities, medications of continuous use, and COVID19 related acute symptoms are provided in the online supplementary material (Table E1-online data supplement).

The mean $_{PEAK}V'O_2$ for the entire study sample was 19.5±5.0ml/kg/min corresponding to 93±21% of $V'O_2$ predicted (30% had $_{PEAK}V'O_2$ ≤80%predicted). $_{PEAK}V'O_2$ tertiles were: ≤17.0, 17.1-22.2 and ≥22.3ml/kg/min. Patients with $_{PEAK}V'O_2$≤17.0ml/kg/min had similar hospitalization severity compared to patients with $_{PEAK}V'O_2$ 17.1-22.2 and ≥22.3ml/kg/min, including days in ICU, need for mechanical ventilation and radiological severity on chest CT at admission. However, at the study follow-up visit (90±10 days after the onset of COVID19), patients with $_{PEAK}V'O_2$≤17.0ml/kg/min reported a greater sensation of dyspnea (mMRC ≥1) compared to the other two groups (Table 2). Additionally, patients with $_{PEAK}V'O_2$≤17.0ml/kg/min had lower forced vital capacity (FVC), total lung capacity (TLC), carbon monoxide diffusion capacity (DLCO), and residual volume (RV) compared to the other groups (Table 2). The persistence of lung

parenchymal involvement on HRCT and cardiac function by echocardiogram at the follow-up visit was similar among groups (Table 2).

CPET findings are presented in Table 3. Patients with $_{PEAK}V'O_2 \leq 17.0$ml/kg/min achieved lower peak work rate (WR), peak heart rate (HR) and lower $\Delta V'O_2/\Delta WR$. At the anaerobic threshold (AT), patients with $_{PEAK}V'O_2 \leq 17.0$ml/kg/min had higher $V'E/V'CO_{2\ AT}$ and lower $PETCO_2$ and no difference on $V'O_2$ (Table 3). Additionally, patients with $_{PEAK}V'O_2 \leq 17.0$ml/kg/min had higher $\Delta V'E/\Delta V'CO_{2RCP}$, peak RR/VT, peak VD/VT, peak $P(a\text{-}ET)CO_2$ and associated with a lower peak arterial oxygen content (CaO_2) and higher level of lactate/WR and a greater sensation of dyspnea and fatigue in proportion to WR compared to patients with $_{PEAK}V'O_2$17.1-22.2 and ≥22.3ml/kg/min (Figure 2).

There was a positive correlation between $_{PEAK}V'O_2$ and FVC, DLCO, V'E/MVV, and peak CaO_2. There was a negative correlation between $_{PEAK}V'O_2$, several comorbidities, dyspnea (mMRC), $\Delta V'E/\Delta V'CO_{2RCP}$, peak RR/VT, peak VD/VT, peak $P(a\text{-}ET)CO_2$, and peak lactate/WR. No correlation was found between $_{PEAK}V'O_2$ and days of hospitalization or in ICU (Table E2-online data supplement).

The ROC curve analyses to identify the presence of a $_{PEAK}V'O_2 \leq 17.0$ml/kg/min, showed a statistically significant AUC for symptoms (mMRC), FVC, DLCO, peak RR/VT, peak V'E/MVV, peak VD/VT, $\Delta V'E/\Delta V'CO_{2RCP}$, $P(a\text{-}ET)CO_2$, peak WR, peak CaO_2, peak lactate and peak lactate/WR. (Table E3-online data supplement).

The univariate logistic regression analysis to predict a $_{PEAK}V'O_2 \leq 17.0$ml/kg/min, including relevant variables from different pathophysiological domains (i.e., symptoms, lung function, ventilatory, gas-exchange, or metabolic responses to exercise) is presented in Table 4. Among non-collinear variables, the multivariate logistic regression model adjusted for age, sex and presence of pulmonary embolism identified that a FVC≤80%predicted and a peak VD/VT≥29 were

independent predictors of a $_{PEAK}V'O_2 \leq 17.0$ml/kg/min (Table 4). A second multivariate logistic regression model was performed, with adjustment for age, sex and the presence of any comorbidity and FVC%predicted and VD/VT remained as predictors of $_{PEAK}V'O_2$ (Table E4 – online data supplement). Of note, VD/VT had a negative correlation with DLCO%predicted (r=0.64, p <0.01), a positive correlation with peak VD (r=0.62, p <0.001) and a positive correlation with P(a-ET)CO_2 (r=0.88, p <0.001). Interestingly, FVC and VD/VT were not significantly correlated (r=0.14, p=0.292).

DISCUSSION:

The present observational study showed that exercise intolerance in post-COVID19 survivors with a relatively short hospital stay (15±10 days) was related to high VD/VT at peak exercise and low FVC%predicted after 90±10 days of acute infection. This finding suggests that both pulmonary microcirculation injury and pulmonary ventilatory impairment might play a role in influencing aerobic capacity in the post-COVID19 survivors.

VD/VT is related to the physiological dead space ratio, divided into anatomical dead space (i.e., airways that do not participate in gas exchange), and alveolar dead space. A high VD/VT results from areas of normal ventilation and low perfusion that contribute to ventilation-perfusion mismatch. A low VD/VT results from areas of low ventilation and normal perfusion. Both high and low VD/VT can be present in the same disease [17]. It is important to note that VD/VT is expected to reach a level below 0.20 after the anaerobic threshold in physiological conditions due to the increased perfusion of areas of the lungs with high ventilation perfusion ratios at rest and a relatively greater increase in tidal volume than anatomical dead space, the abnormal response is dependent on severity of pulmonary lesions [16]. In our sample, VD/VT decreased during exercise in all three groups. But peak VD/VT progressively increased from the

subgroup $_{PEAK}V'O_2$>22.2ml/kg/min to the subgroup $_{PEAK}V'O_2$≤17.0ml/kg/min. Additionally, despite reducing during exercise, VD/VT did not reach physiological values in all three groups. A high VD/VT might be related to ventilatory inefficiency (high $V'E/V'CO_2$), and dyspnea sensation, being associated or not with enhanced chemosensitivity and a decreased CO_2 set point [17].

Our results show that a high VD/VT at peak exercise (≥0.29) is an independent predictor of a $_{PEAK}V'O_2$≤17.0ml/min/kg (Table 4). In addition to the high VD/VT, a high peak exercise P(a-ET)CO_2 (Figure 2) might corroborate the presence of V/Q inequality in the studied population. Some studies in post-COVID19 patients showed an increase in VD/VT; however, they did not link its association to patients' exercise intolerance [11, 18]. Baratto et al. showed that exercise hyperventilation after COVID19 acute infection was related to enhanced chemoreflex sensitivity rather than increased VD/VT [11]. Conversely, others have demonstrated that a reduced $_{PEAK}V'O_2$ was associated with a mild increase of $V'E/V'CO_2$ and have suggested that the observed hyperventilation could be related to increased chemoreflex sensitivity secondary to deconditioning, dysfunctional breathing, or even dysautonomia [6, 9, 19, 20]. Acute COVID19 lung lesions have been related to diffuse alveolar damage (DAD), interstitial fibrosis and endothelial vascular injuries, which result in areas of shunt (low V/Q) and/or dead space (high V/Q). Along the lines, studies comparing ARDS in COVID19 vs. non-COVID19 patients showed that COVID19 ARDS patients have a higher dead space ventilation compared to non-COVID19-ARDS, despite a similar pulmonary compliance [21]. The aforementioned lung insults can potentially cause transitory or persistent lung sequelae [22–24]. In our study, VD/VT had a negative correlation with low DLCO, a positive correlation with VD, and a positive correlation with P(a-ET)CO_2. Similar findings have been shown for cardiocirculatory diseases such as left heart failure and pulmonary arterial hypertension [25–28]. It is important to note that a low DLCO was found in the long term after SARS-COV1 and SARS-COV2 patients, even in those with normal lung

parenchyma on HRCT [2, 29–33]. Furthermore, during acute COVID19 infection, dual-energy thoracic CT studies showed the presence of pulmonary perfusion heterogeneity along with pulmonary ischemic areas in the absence of visible pulmonary arterial thrombosis and in areas not related to ground glass opacities or any parenchymal lesions, which may reflect the presence of microvascular injury [34]. Based on the above and our study findings, we speculate that chronic lung microvascular injury might be a pathophysiological mechanism leading to high VD/VT during exercise in post-COVID19 patients. This hypothesis is supported by the multivariate regression (Table 4), where pulmonary embolism was not a determining factor for the increased VD/VT. The same occurs when the regression is adjusted for the presence of any comorbidity (Tabe E4–online data supplement), suggesting that VD/VT might be elevated due to microcirculation injury. Of note, this microvascular involvement had no repercussions on the findings of resting echocardiogram in our patients.

FVC%predicted was also identified as an independent predictor of a $_{PEAK}V'O_2 \leq 17.0$ml/kg/min; however, FVC and VD/VT were not significantly correlated. A low FVC has been reported in post-COVID19 patients as far as one year after the acute infection, and similar results have been demonstrated in SARS-COV1 survivors [29, 33]. Considering that a low FVC might be related to the acute respiratory distress syndrome severity, it might indicate the development of restrictive ventilatory impairment secondary to lung interstitial sequelae [35]. This is in line with a tachypnea pattern, proven by high RR/VT. Nonetheless, we did not identify significant differences in TLC and acute parenchymal lung involvement on HRCT according to $_{PEAK}V'O_2$ severity (Table 2).

In addition to a potential interstitial lung disease development impacting FVC, we should also consider pulmonary neuromuscular dysfunction as a possible cause of reduced FVC. Inspiratory muscle weakness and decreases in peripheral muscle strength have been described in

post-COVID19 patients and were associated with reduced aerobic capacity [35–37]. However, our results did not identify a significant difference in maximal inspiratory pressure according to $_{PEAK}V'O_2$ severity (Table 2).

Interestingly, lactate/WR was higher according to $V'O_2$ tertiles (Figure 2), despite the similar anaerobic threshold (Table 3). This finding has been previously demonstrated in patients with oxidative myopathy [38]. It suggests that the mechanisms of lactate clearance fail to keep pace with lactate production in post-COVID19 patients, and/or there is an impairment in O_2 utilization at higher levels of exercise [39]. In our study, the elevated lactate/WR observed in patients with $_{PEAK}V'O_2 \leq 17.0$ml/kg/min might be a consequence of a mildly reduced O_2 delivery (low CaO_2) and/or an imbalance in O_2 muscle utilization due to a decrease in oxidative fibers secondary to prolonged hospitalization, neuromuscular drug toxicity, direct viral mitochondrial injury by immediate viral effect and/or systemic inflammation [3, 40]. As a result, the aforementioned mechanisms will stimulate a rapid respiratory rate and increase the neural perception of dyspnea, but further studies are required to investigate this hypothesis in post-COVID19 patients.

Our study has some limitations that should be considered. We did not include a healthy-control group; nonetheless patients with $_{PEAK}V'O_2 > 22.2$ml/kg/min had a more preserved aerobic capacity and therefore could be considered from an exercise physiology perspective as a control for the subgroup with $_{PEAK}V'O_2 \leq 17.0$ml/kg/min. Despite not having a health control group, our exercise findings are similar to Skjørten et al. [6]. Along these lines, it is important to note that all patients included in the subgroup $_{PEAK}V'O_2$22.2ml/kg/min had a $_{PEAK}V'O_2$>80%pred, and that most patients with a $V'O_2 \leq 80\%$predicted were included in the subgroup $_{PEAK}V'O_2 \leq 17.0$ ml/kg/min. In physiological terms, the $V'O_2$ in absolute value decreases with aging and more in females than males. In our study, age was different across $_{PEAK}V'O_2$ subgroups. It is known that age and sex

might influence some ventilatory responses due to lower VT_{PEAK} and less efficient ventilation during exercise (without abnormally high VD/VT), likely related to increased airway resistance and mechanical constraint with a reduced compliance of the lungs. This phenomenon is more pronounced in older females but, in general, with little impact on exercise capacity. Of note, sex per se does not affect gas exchange, but indeed ageing could change the $PaCO_2$ equilibrium [41, 42]. Considering this and aiming to minimize the possible effects of age and sex on exercise physiological responses and in the study findings, the multivariate model was adjusted for age and sex. We did not perform exercise hemodynamics, single-photon emission lung CT or dual-energy CT thoracic angiography and therefore, we can only speculate on the association between high VD/VT during exercise and the hypothesis of pulmonary microvascular dysfunction. Additionally, we did not perform comprehensive muscle-related studies, and therefore, we are not able to undoubtedly muscle weakness as a potential cause for a reduced $_{PEAK}V'O_2$. Finally, the control of breathing during exercise is complex, multifactorial, and not completely understood. The current study could not explain or phenotype the pathophysiological mechanisms of exercise intolerance in post-COVID19 patients.

In summary, the current study demonstrates that a high VD/VT at peak exercise and a low resting FVC are associated with a reduced $_{PEAK}V'O_2$ in moderate-to-severe/critical post-COVID19 patients. The high peak exercise VD/VT might suggest the role of pulmonary microvascular dysfunction on dyspnea and exercise intolerance in the post-COVID19 survivors. The low FVC suggests that pulmonary ventilatory dysfunction might be an additional factor influencing aerobic capacity in this patient population. Further studies are needed to confirm if patients with the post-COVID19 survivors will develop pulmonary vascular disease and/or clinically relevant interstitial pulmonary disease in the long term.

Acknowledgements: The authors thank all participating investigators of the SEFICE (Pulmonary Function and Clinical Exercise Physiology Sector) from the Hospital Sao Paulo – UNIFESP/EPM for their contribution to the collected data and review of the article.

Conflict of interest: Mariana L Lafetá has nothing to disclose. Vitor C Souza has nothing to disclose. Thaís C F Menezes has nothing to disclose. Carlos G Y Verrastro has nothing to disclose. Frederico J Mancuso has nothing to disclose. André Luis P Albuquerque has nothing to disclose. Suzana E Tanni reports be President of Sao Paulo Thoracic Society, outside the submitted work. Meyer Izbicki has nothing to disclose. Júlio P Carlstron has nothing to disclose. Luiz Eduardo Nery has nothing to disclose. Rudolf K F Oliveira report grants from National Council for Scientific and Technological Development (CNPq, Brazil, grant 313284/2021-0) and personal fees from Janssen Brazil, outside the submitted work. Priscila A Sperandio has nothing to disclose. Eloara V M Ferreira reports speaker fees from Janssen, and personal fees from Aché, Aztrazeneca, Bayer, Boeringer, GSK, Novo Nordisk, Jassen-Cilag J&J, Zambon, outside the submitted work.

Support statement: This study was supported by Sao Paulo Research Foundation (Fapesp) (protocol number: 2020/08996-1) and Mariana Lima Lafetá receives a PhD bursary from CAPES (Coordination for Improvement of Higher Education Personnel) (process number: 88887.508806/2020-00).

TABLES:

Table 1. COVID19 patient's baseline characteristics.

	Total (n=87)
Male gender	54 (62)
Age, yrs	53 ± 13
BMI, kg/m^2	30 ± 4
Comorbidities	
No comorbidity	6 (7)
One comorbidity	25 (29)
≥ 2 comorbidities	55 (63)
Hospitalization	
Hospital days	15 ± 10
Patients in ICU	52 (54)
Days in ICU	12 ± 10
Oxygen supplementation device	
Nasal cannula or mask	42 (48)
NIV or HFNC	25 (29)
Mechanical ventilation	21 (24)
Chest HRCT at admission	
Groud glass ≥ 50%	43 (49.5)
Laboratory results at hospital admission	
SpO_2 ,%	87 ± 7
Lymphocytes, uL	1071 ± 638
C-RP, mg/L	128 ± 74
D-Dimer, mcg/mL	2.5 ± 3.5
PaO_2 , mmHg	57 ± 11
$PaCO_2$, mmHg	32 ± 5
SaO_2 ,%	89 ± 5
Drug therapy during hospitalization	
Corticosteroids	78 (90)

Prophylactic anticoagulation	83 (95)
Therapeutic anticoagulation	21 (24)
Cardiovascular complications	
Pulmonary embolism (PE)	12 (14)
Myocarditis/Cardiomyopathy	8 (9)

Data are presented as an absolute value and percentage *(n* %) or mean ± standard deviation. *Definition of abbreviation:* BMI: body mass index; ICU: intensive care unit; NIV: non-invasive ventilation; HFNC: high flow nasal cannula; Chest HRCT: chest high resolution computed tomography; SpO_2: pulse oxygen saturation; C-RP: C-reactive protein; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; SaO_2: arterial oxygen saturation.

Table 2. COVID19 patients' characteristics during hospitalization and lung function tests, chest tomography and echocardiogram according to $_{PEAK}V'O_2$ (ml/kg/min) tertiles.

	Total (n=87)	$_{PEAK}V'O_2$ ≤ 17.0 ml/kg/min (n=29)	$_{PEAK}V'O_2$ 17.1-22.2 ml/kg/min (n=29)	$_{PEAK}V'O_2$ ≥ 22.3 ml/kg/min (n=29)	*p* Values
Male	55 (63)	11 (37) *	17 (59) ‡	27 (93)	<0.001
Age, yrs	53 ± 13	60 ± 11 *†	52 ± 13	46 ± 10	<0.001
BMI (kg/m^2)	29.8 ± 4	29.6 ± 4	30.3 ± 5	29.6 ± 3	0.786
Severity during hospitalization					
Days in ICU	12 ± 10	15 ± 14	13 ± 13	11 ± 8	0.583
Mechanical ventilation	21 (24)	6 (21)	7 (24)	8 (28)	0.660
Chest HRCT - GGO ≥ 50%	43 (49.5)	17 (59)	14 (48)	12 (41)	0.400
Pulmonary Embolism	12 (14)	5 (17)	3 (10)	4 (15)	0.755
Follow-up visit §					
Symptoms *§*					
mMRC ≥ 1	60 (69)	27 (93) *	21 (72) ‡	12 (41)	<0.001
Fatigue / Myalgia	45 (52)	17 (59)	16 (55)	12 (41)	0.389
Memory loss	26 (30)	12 (41)	10 (34)	4 (14)	0.058
No symptoms	17 (20)	1 (3) *	4 (14) ‡	12 (41)	0.001
Lung function §					
FVC, %pred	88 ± 13	81 ± 12 †	91 ± 14	90 ± 13	0.024
FEV1, %pred	90 ± 13	85 ± 12	92 ± 13	92 ± 14	0.127
FEV1/FVC	0.82 ± 0.50	0.83 ± 0.60	0.81 ± 0.40	0.83 ± 0.40	0.241
DLCO, %pred	80 ± 23	66 ± 25 †	86 ± 21	84 ± 19	0.021
DLCO/VA, % pred	101 ± 22	91 ± 27	102 ± 21	108 ± 18	0.077
TLC, %pred	84 ± 14	81 ± 17	88 ± 12	83 ± 12	0.247
RV, %pred	97 ± 26	102 ± 37	105 ± 22 ‡	87 ± 19	0.045

MIP, %pred	105 ± 23	96 ± 29	110 ± 21	109 ± 21	0.174
MEP, %pred	97 ± 25	87 ± 23	99 ± 28	108 ± 22	0.059
Echocardiogram §					
Left ventricular ejection fraction,%	65 ± 7	63 ± 8	65 ± 7	66 ± 5	0.508
TRV, m/s	2.3 ± 0.2	2.3 ± 0.3	2.5 ± 0.1	2.1 ± 0.3	0.417
sPAP, mmHg	27 ± 8	29 ± 6	31 ± 3	20 ± 8	0.083
Chest HRCT §					
Near-Normal, ≤ 10 %	68 (76)	19 (66)	28 (96)	21 (72)	0.833
Abnormalities ≥ 25%	14 (16)	4 (14)	7 (24)	3 (10)	0.565

Data are presented as an absolute value and percentage *(n* %) or mean ± standard deviation. Definition of abbreviations: ICU: intensive care unit; HRCT: high resolution computed tomography; GGO: ground glass opacity; FVC: forced vital capacity; FEV1: forced expiratory volume in first second; DLCO: diffusing capacity of the lung for carbon monoxide; VA: alveolar volume; TLC: total lung capacity; RV: residual volume; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; TRV: tricuspid valve regurgitation; sPAP: systolic pulmonary artery pressure. p-values from ANOVA or Kruskall-Wallis and difference between groups by $_{PEAK}V'O_2$ (ml/kg/min): * ≤ 17.0 vs. ≥ 22.3; † ≤ 17.0 vs. 17.1 – 22.2; ‡ 17.1 – 22.2 vs. ≥ 22.3 ml/kg/min. § 90 ± 10 days after hospitalization and total of patients who underwent spirometry (n=78), lung volumes (n=64), DLCO and muscle strength (n=54), echocardiogram (n=74), chest HRCT (n=87). Other symptoms: cough (16%), headache (14%), depressed mood (13%), insomnia (13%), chest pain (10%).

Table 3. COVID19 patients CPET responses and blood gas analysis at rest and at peak exercise according to $_{PEAK}$ V'O_2 (ml/kg/min) tertiles.

		$_{PEAK}$ V'O_2			
	Total (n=87)	**≤ 17.0 ml/kg/min** (n=29)	**17.1-22.2 ml/kg/min** (n=29)	**≥ 22.3 ml/kg/min** (n=29)	***p* Values**
CPET responses					
Peak V'O_2, % pred	93 ± 21	80 ± 18 *†	96 ± 18	103 ± 19	<0.001
Peak WR, W	108 ± 46	68 ± 22 *†	104 ± 34 ‡	152 ± 33	<0.001
Peak RER	1.10 ± 0.12	1.10 ± 0.11	1.08 ± 0.14	1.12 ± 0.11	0.374
Peak HR, % pred	87 ± 12	79 ± 12 *†	90 ± 10	93 ± 9	<0.001
V'O_2 AT, % pred	56 ± 15	52 ± 16	60 ± 16	55 ± 14	0.196
ΔV'O_2/ΔWR, ml/min/W	11 ± 2	11 ± 1 *	12 ± 2	12 ± 2	0.014
Peak V'O_2/HR, %pred	108 ± 24	105 ±26	107 ± 26	111 ± 21	0.620
Peak V'E/MVV	0.53 ± 0.14	0.48 ± 0.15 *	0.54 ± 0.14	0.58 ± 0.10	0.028
Peak VT, L	1.54 ± 0.49	1.18 ± 0.35 *†	1.55 ± 0.42 ‡	1.89 ± 0.44	<0.001
Peak RR/VT	26 ± 14	33 ± 20 *	24 ± 9	23 ± 9	0.017
V'E/V'CO_2 AT	33 ± 6	36 ± 6 *	33 ± 6 ‡	29 ± 4	<0.001
Peak V'E/ V'CO_2	38 ± 8	41 ± 9 *	38 ± 8	35 ± 5	0.012
$PETCO_2$ AT, mmHg	38 ± 5	36 ± 4 *	38 ± 6 ‡	41 ± 4	<0.001
Peak$PETCO_2$,mmHg	33 ± 5	31 ± 5 *	33 ± 6	34 ± 4	0.039
Rest SpO_2, %	97 ± 1	96 ± 2	97 ± 1	97 ± 1	0.205
Peak SpO_2, %	95 ± 3	95 ± 4	95 ± 3	95 ± 3	0.900
Blood Gas Analysis					
Rest VD/VT	0.40 ± 0.09	0.45 ± 0.09 *	0.38 ± 0.09	0.38 ± 0.07	0.035
Peak VD/VT	0.26 ± 0.12	0.34 ± 0.12 *†	0.25 ± 0.12	0.21 ± 0.10	<0.001
Rest P(A-a) O_2, mmHg	12 (10 -14)	14 (11 -18) *	13 (10 - 16)	9 (6 -12)	0.025

Peak P(A-a) O_2, mmHg	26 (19 - 34)	31 (22 - 36)	24 (16 - 31)	24 (18 - 31)	0.498
Rest CaO_2, mL/dL	19.5 ± 2	18.6 ± 3 *	19.7 ± 2	20.2 ± 2	0.042
Peak CaO_2, mL/dL	21.7 ± 3	20.5 ± 3 *	21.7 ± 2	22.6 ± 3	0.034
Rest PaO_2, mmHg	79 ± 8	79 ± 9	78 ± 9	80 ± 7	0.849
Peak PaO_2, mmHg	80 ± 12	77 ± 14	82 ± 10	81 ± 13	0.569
Rest $PaCO_2$, mmHg	35 ± 4	35 ± 3	34 ± 4 ‡	37 ± 4	0.035
Peak $PaCO_2$,mmHg	33 ± 4	33 ± 4	32 ± 4	34 ± 3	0.188
Hb, mg/dL	14.9 ± 2.0	14.2 ± 2.0	15.2 ± 1.0	15.3 ± 2.0	0.053

Data are presented as mean ± standard deviation or medians (IQRs). Definition of abbreviation: $V'O_2$: oxygen uptake; WR: work rate; RER: respiratory exchange ratio; HR: heart rate; AT: anaerobic threshold; V'E: minute ventilation; VT: tidal volume; RR: respiratory rate; $PETCO_2$: end-tidal carbon dioxide pressure; MVV: maximal voluntary ventilation; $V'CO_2$: carbon dioxide output; SpO_2: pulse oxygen saturation; VD/VT: dead space fraction of tidal volume; P(A-a) O_2: alveolar-arterial oxygen difference; CaO_2: arterial oxygen content; PaO_2: arterial oxygen partial pressure; $PaCO_2$: arterial carbon dioxide partial pressure; Hb: hemoglobin; p-values from ANOVA or Kruskall-Wallis and difference between groups by $_{PEAK}V'O_2$ * ≤ 17.0 and ≥ 22.3; † ≤ 17 and 17.1 – 22.2; ‡ 17.1 – 22.2 and ≥ 22.3 ml/kg/min.

Table 4. Univariate and multivariate logistic analysis adjusted for sex, age and pulmonary embolism for $_{PEAK}V'O_2 \leq 17.0$ ml/kg/min according to persistence of symptoms, lung function and CPET variables.

Variables		UNIVARIATE			MULTIVARIATE		
		***p* Values**	**Odds**	**IC**	***p* Values**	**Odds**	**IC**
Symptoms	mMRC ≥ 1	0.015	3.90	1.30 – 11.64			
Lung Function	FVC ≤ 80, % pred	<0.001	9.49	2.96 – 30.39	0.004	17.32	2.53 – 118.32
	DLCO ≤ 65, % pred	0.002	9.60	2.37 – 38.86			
CPET							
Ventilatory responses	Peak V'E/MVV ≥ 49	0.005	0.25	0.10 – 0.66			
	Peak RR/VT ≥ 40	<0.001	5.83	2.10 – 16.14			
Gas-exchange responses	$\Delta V'E/\Delta V'CO_{2RCP} \geq 32$	0.001	4.87	1.83 – 12.95			
	Peak VD/VT ≥ 29	<0.001	20.30	4.08 -100.98	0.004	26.57	2.84 – 248.61
	Peak $P(a\text{-}ET)CO_2 \geq$ 2.65	0.001	7.50	2.20 – 25.57			
Metabolic responses	$\Delta V'O_2/\Delta WR \leq 11.5$, mL/min/watts	0.012	4.10	1.36 – 12.32			
	Lactate/WR ≥ 0.075, mmol/L/watts	<0.001	10.28	3.01 – 35.13			

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 output; RCP: respiratory compensation point; VD/VT= dead space fraction of tidal volume; $P(a\text{-}ET)CO_2$: arterial to End-tidal cardon dioxide difference; WR: work rate (watts). Multivariate logistic analysis , with $R^2 = 0.46$. Cutoff point of the variables defined by ROC Curve

REFERENCES:

1. Special Epidemiological Bulletin: COVID-19. Ministry of Health. Brazil, 2021. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/boletins-epidemiologicos/covid-19/2021/boletim_epidemiologico_covid_90_30nov21_eapv5.pdf.

2. Huang L, Yao Q, Gu X, *et at.* 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021 Aug 28;398(10302):747-758.

3. Nalbandian A, Sehgal K, Gupta A, *et al*. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615.

4. Rinaldo RF, Mondoni M, Parazzini EM, *et al*. Severity does not impact on exercise capacity in COVID-19 survivors. *Respir Med* 2021;187:106577.

5. Garrigues E, Janvier P, Kherabi Y, *et al*. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect. 2020 Dec;81(6):e4-e6.

6. Skjørten I, Ankerstjerne OAW, Trebinjac D, *et al*. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalization. Eur Respir J. 2021 Aug 26;58(2):2100996.

7. Rinaldo RF, Mondoni M, Parazzini EM, *et al*. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. Eur Respir J; 58(2)2021 08.

8. Daniels CJ, Rajpal S, Greenshields JT, *et al*. Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes with Recent SARS-CoV-2 Infection: Results from the Big Ten COVID-19 Cardiac Registry. *JAMA Cardiol* 2021;6:1078–1087.

9. Dorelli G, Braggio M, Gabbiani D, *et al*. Importance of Cardiopulmonary Exercise Testing amongst Subjects Recovering from COVID-19. Diagnostics (Basel). 2021 Mar 12;11(3):507.

10. Lashgari R, De Vito EL, Avanaki K, *et al*. Survivors Seven Months After Recovery. Frontiers in Medicine. 8. 636298. Available from: 10.3389/fmed.2021.636298.

11. Baratto C, Caravita S, Faini A, *et al*. Impact of COVID-19 on exercise pathophysiology: a

combined cardiopulmonary and echocardiographic exercise study. J Appl Physiol (1985). 2021 May 1;130(5):1470-1478.

12. Singh I, Joseph P, Heerdt PM, *et al.* Persistent Exertional Intolerance After COVID-19 Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2022 Jan;161(1):54-63.

13. Neder JA, Andreoni S, Castelo-Filho A, *et al.* Reference values for lung function tests. I. Static volumes. Braz J Med Biol Res. 1999 Jun;32(6):703-17.

14. Neder JA, Andreoni S, Peres C, *et al.* Reference values for lung function tests. III. Carbon monoxide diffusing capacity (transfer factor). Braz J Med Biol Res. 1999 Jun;32(6):729-37.

15. Myllärniemi M, Saarto T. mMRC dyspnoea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. ERJ Open Res. 2017 Dec 14;3(4):00084-2017.

16. Neder JA, Berton DC, Rocha A, *et al.* Abnormal patterns of response to incremental CPET. Clin Exerc Test Sheffield, United Kingdom: European Respiratory Society; 2018. p. 34–58.

17. Weatherald J, Sattler C, Garcia G, *et al.* Ventilatory response to exercise in cardiopulmonary disease: The role of chemosensitivity and dead space. Eur Respir J. 2018 Feb 7;51(2):1700860.

18. Frésard I, Genecand L, Altarelli M, *et al*. Dysfunctional breathing diagnosed by cardiopulmonary exercise testing in “long COVID” patients with persistent dyspnoea. BMJ Open Respir Res. 2022 Mar;9(1):e001126.

19. Motiejunaite J, Balagny P, Arnoult F, *et al*. Hyperventilation as one of the mechanisms of persistent dyspnoea in SARS-CoV-2 survivors. Eur Respir J. 2021 Aug 26;58(2):2101578.

20. Mancini DM, Brunjes DL, Lala A, *et al*. Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post–Coronavirus Disease. ACC Heart Fail. 2021 Dec;9(12):927-937.

21. Bertelli M, Fusina F, Prezioso C *et al*. COVID-19 ARDS Is Characterized by Increased Dead

Space Ventilation Compared With Non-COVID ARDS. *Respir Care* 2021; 66(9): 1406–1415.

22. Polak SB, Van Gool IC, Cohen D. *et al*. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol 33, 2128–2138 (2020).

23. Guo L, Jin Z, Gan TJ, Wang E. Silent hypoxemia in patients with covid-19 pneumonia: A review. Med Sci Monit. 2021 Oct 12;27:e930776.

24. Baldi BG, Fabro AT, Franco AC, *et al*. Clinical, radiological, and transbronchial biopsy findings in patients with long COVID-19: a case series. J Bras Pneumol. 2022 Apr 29;48(3):e20210438.

25. Wasserman K, Zhang YY, Gitt A, *et al.* Lung function and exercise gas exchange in chronic heart failure. Circulation. 1997 Oct 7;96(7):2221-7.

26. Kee K, Stuart-Andrews C, Ellis MJ, *et al.* Increased dead space ventilation mediates reduced exercise capacity in systolic heart failure. Am J Respir Crit Care Med. 2016 Jun 1;193(11):1292-300.

27. Dantzker DR, Bower JS. Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. Clin Invest. 1979 Oct;64(4):1050-5.

28. Laveneziana P, Montani D, Dorfmüller P, *et al.* Mechanisms of exertional dyspnoea in pulmonary veno-occlusive disease with EIF2AK4 mutations. Eur Respir J. 2014 Oct;44(4):1069-72.

29. Ong KC, Ng AW, Lee LS, *et al*. Pulmonary function and exercise capacity in survivors of severe acute respiratory syndrome. Eur Respir J. 2004 Sep;24(3):436-42.

30. Guler SA, Ebner L, Aubry-Beigelman C, *et al.* Pulmonary function and radiological features 4 months after COVID-19: First results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J. 2021 Apr 29;57(4):2003690.

31. Wu X, Liu X, Zhou Y, *et al*. 3-month, 6-month, 9-month, and 12-month respiratory

outcomes in patients following COVID-19-related hospitalisation: a prospective study. Lancet Respir Med. 2021 Jul;9(7):747-754.

32. Sonnweber T, Sahanic S, Pizzini A, *et al*. Cardiopulmonary recovery after COVID-19: An observational prospective multicentre trial. Eur Respir J. 2021 Apr 29;57(4):2003481.

33. Hui DS, Wong KT, Ko FW, *et al.* The 1-Year Impact of Severe Acute Respiratory Syndrome on Pulmonary Function, Exercise Capacity, and Quality of Life in a Cohort of Survivors. Chest. 2005 Oct;128(4):2247-61.

34. Grillet F, Busse-Coté A, Calame P, *et al*. COVID-19 pneumonia: Microvascular disease revealed on pulmonary dual-energy computed tomography angiography. Quant Imaging Med Surg. 2020 Sep;10(9):1852-1862.

35. Mancuzo EV, Marinho CC, Machado-Coelho GLL, *et al.* Lung function of patients hospitalized with COVID-19 at 45 days after hospital discharge: first report of a prospective multicenter study in Brazil. J Bras Pneumol. 2021; 47(6): e20210162.

36. Acar RD, Saribaş E, Güney PA, *et al.* COVID-19: The new cause of dyspnoea as a result of reduced lung and peripheral muscle performance. J Breath Res. 2021 Oct 4;15(4).

37. Clavario P, De Marzo V, Lotti R, *et al.* Cardiopulmonary exercise testing in COVID-19 patients at 3 months. Int J Cardiol. 2021 Oct 1;340:113-118.

38. Vanuxem P, Vanuxem D, Raharison L, *et al*. Maximal exercise and muscle energy metabolism after recovery from exercise hyperthermia syndrome. Muscle Nerve, 24: 1071-1077.

39. B Brooks GA. Anaerobic threshold, Medicine & Science in Sports & Exercise: February 1985 - Volume 17 - Issue 1 - p 22-31.

40. Rodriguez B, Nansoz S, Cameron DR, *et al*. Is myopathy part of long-Covid? Clin Neurophysiol. 2021 Jun;132(6):1241-1242.

41. Schaeffer MR, Guenette JA, Jensen D. Impact of ageing and pregnancy on the minute

ventilation/carbon dioxide production response to exercise. *Eur Respir Rev*. 2021;30(161):200225.

42. Dominelli PB, Molgat-Seon Y. Sex, gender and the pulmonary physiology of exercise. *Eur Respir Rev*. 2022;31(163):210074.

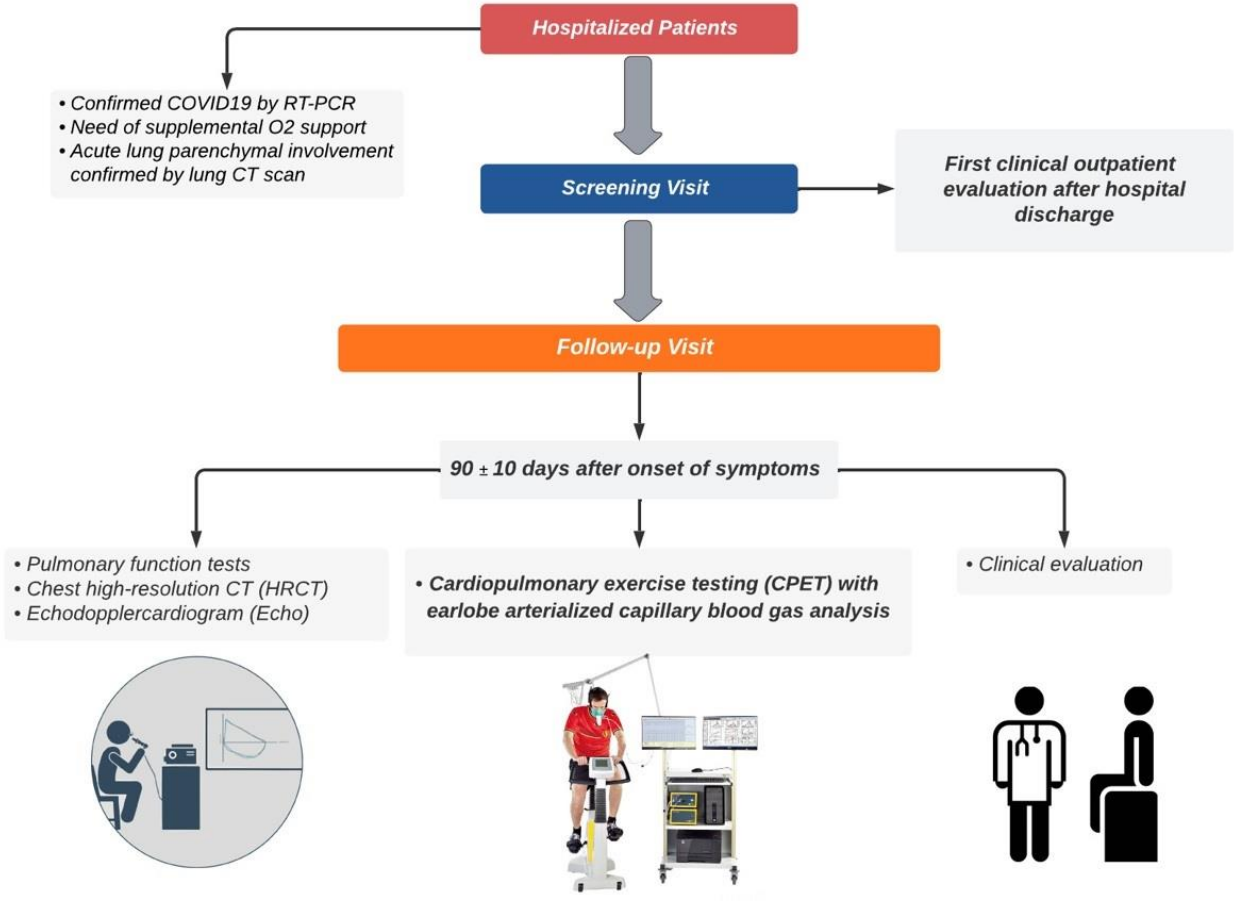

Figure 1. Patients' inclusion and study protocol.

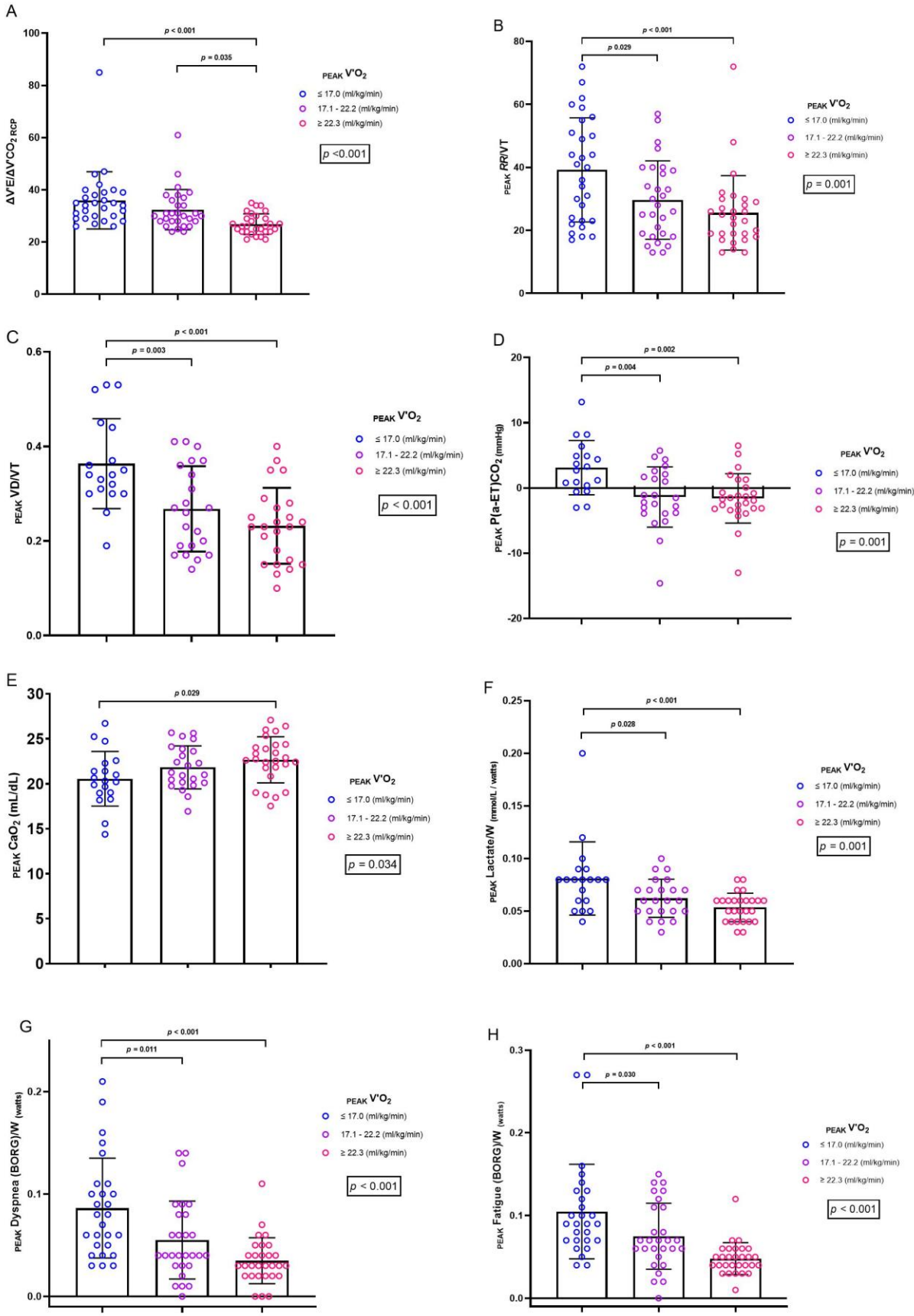

Figure 2. Comparison of PEAKV'O2 (ml/kg/min) in CPET responses after 3 months of symptoms in

survivors of COVID19. (A) ?V'E/?V'CO2RCP = ventilatory equivalents for carbon dioxide at respiratory compensation point; (B) PEAK RR/VT= respiratory rate of tidal volume at peak exercise; (C) PEAK VD/VT= dead space fraction of tidal volume at peak exercise; (D) PEAKP(a-ET)CO2= arterial to End-tidal carbon dioxide difference at peak exercise; (E) PEAK CaO2 = relation of V'O2 and arterial oxygen content at peak exercise; (F) PEAK Lactate/W= lactate by work rate at peak exercise; (G)) PEAK BORG/W= Dyspnea BORG scale by work rate at peak exercise; (H) PEAK BORG/W= Fatigue BORG scale by work rate at peak exercise. p-value (ANOVA or Kruskall-Wallis)

Exercise intolerance in post-COVID19 survivors after hospitalization

Online Data Supplement

Mariana L Lafetá [1], Vitor C Souza[1], Thaís C F Menezes[1], Carlos G Y Verrastro[5], Frederico J Mancuso[2], André Luis P Albuquerque[4], Suzana E Tanni[3], Meyer Izbicki[1], Júlio P Carlstron[1], Luiz Eduardo Nery[1], Rudolf K F Oliveira[1], Priscila A Sperandio[1], Eloara V M Ferreira[1]

[1] Pulmonary Function and Clinical Exercise Physiology Unit (SEFICE), Division of Respiratory Diseases, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

[2] Division of Cardiology, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

[3] Division of Internal Medicine of Botucatu Medical School, São Paulo State University-UNESP, Botucatu, Brazil.

[4] Pulmonary Division, Heart Institute (INCOR), Clinical Hospital HCFMUSP, Faculty of the Medicine University of Sao Paulo, Sao Paulo, Brazil; Sírio-Libanês Teaching and Research Institute, São Paulo, Brazil

[5] Radiology Division, Federal University of Sao Paulo (UNIFESP), Sao Paulo, Brazil

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 $\Delta V'CO_2$ ratio ($\Delta V'E/\Delta V'CO_2$) 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 ≥1.10; the peak of heart rate (HR) ≥ 85% pred or a rate of perceived exertion ≥ 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.

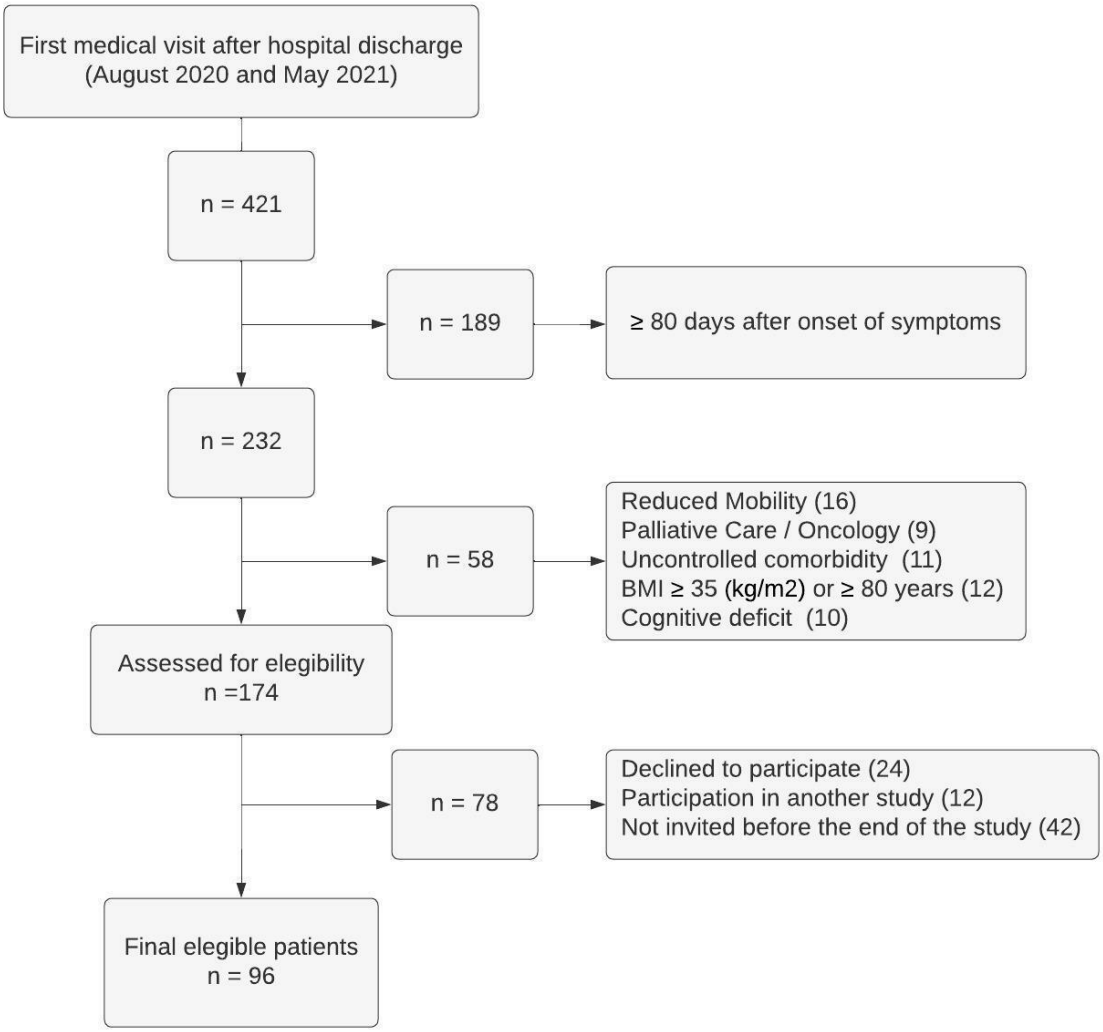

Figure E1. Enrollment of patients at first medical visit after hospital discharge.

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

	Total (n=87)		Total (n=87)
Comorbidities		**Acute symptoms at hospital admission**	
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
$\Delta V'E/\Delta V'CO_{2RCP}$	-0.45	<0.001
Peak VD/VT	-0.44	<0.001
Peak $P(A\text{-}a)O_2$, mmHg	-0.07	0.553
Peak $P(a\text{-}ET)CO_2$, mmHg	-0.35	0.003
Peak WR, watts	0.78	<0.001
$\Delta V'O_2/\Delta WR$, 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; $P(A\text{-}a)O_2$: alveolar-arterial oxygen difference; VD/VT: dead space fraction of tidal volume; $P(a\text{-}ET)CO_2$: 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.