AUGUSTO MOTTA UNIVERSITY CENTER
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EFFECTS OF PILATES ON PERIPHERAL MUSCLE STRENGTH, DYSPNEA AND FATIGUE IN PATIENTS WITH POST-COVID-19 SYNDROME: CONTROLLED AND RANZOMIZED CLINICAL TRIAL

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Summary

Introduction: COVID-19 is an emerging pandemic disease caused by severe acute respiratory syndrome (SARS-CoV-2). Although most patients infected with SARS-CoV-2 are asymptomatic or have mild symptoms, some patients develop severe symptoms that can long-term impair their quality of life and functional capacity. SARS-CoV-2 is closely related to severe acute respiratory syndrome (SARS) with direct and indirect effects on several systems, especially the musculoskeletal system, in addition to the respiratory system. Some of these symptoms persist for a long time, called Post-Covid-19 Syndrome, directly interfering with the functional capacity and quality of life of these patients. Pilates exercises focus on breathing, postural symmetry, trunk stabilization, flexibility, joint mobility and strengthening through the full range of motion of all joints and not isolated muscle groups. **Objectives:** The objective of this study will be to evaluate the clinical and functional effects of a Pilates exercise program for patients with Post-Covid-19 syndrome after a period of intensive care admission and invasive mechanical ventilation. **Methods:** The study will be a clinical, randomized and controlled trial. 48 patients of both sexes, over 18 years of age, who have developed the severe form of COVID-19 and required at least 7 days of invasive mechanical ventilation will be recruited. Patients who currently require supplemental oxygen at home and who present motor, cognitive or neurological alterations that prevent the practice of Pilates will be excluded . They will be previously randomized in a 1:1 ratio by electronic system and blindly allocated to the intervention group that will perform an exercise protocol based on the Pilates method , 2x/week, for 12 weeks in therapeutic sessions of identical protocols lasting 60 min. All patients will be evaluated before and after for peripheral muscle strength and endurance , post-Covid-19 functional status, dyspnea, fatigue and quality of life. Data analysis will be performed using the SPSS 23.0 program (*Statistical Package for Social Sciences*). Descriptive analysis will be performed for all variables (mean and standard deviation). *General Linear Model* (GLMs) with mixed design will be performed to compare treatment effect size between groups. The *pairwise comparison comparisons*) will be performed to verify the mean difference between the Pilates Group and the Control Group in all variables in each period independently. Intention-to-treat analysis was used using the *Last method. observation Carried Forward* (LOCF) for lost participant data. A significance level of 0.05 and a confidence interval of 95% will be adopted. **Results:** The expected results are based on the alternative hypothesis that Pilates exercises are clinically effective, improving functional performance, exercise tolerance, balance , reducing symptoms and improving the quality of life of patients with symptoms of Post-Covid-19 Syndrome.

Keywords: Covid-19; Pilates Method ; everyday activities; (http://decs.bvs.br/).

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Capítulo 1 Literature review

1.1 Introduction

Covid-19 has been described as a serious respiratory disease, which mainly affects the lower respiratory tract, coursing with pneumonia and SARS. In general, the course of the disease can range from mild (about 81% of cases) or moderate to severe (14% of cases) (MACHADO, *et al.* , 2020; RAGHU, WILSON, 2020) . However, about 5% have critical clinical conditions combined with other systemic complications, as a result of the morbidities acquired in the process, which cause important impacts on the functional and cognitive capacities of recovered individuals (PAHO/WHO, 2020)

In this context, the respiratory condition is one of the most affected in the process of infection by SARS-CoV-2, and such findings have been demonstrated by studies with very robust methodologies, that important fibrotic lung lesions emerged as the main consequences observed in individuals who had the most severe form of Covid-19 (GREVE, BRECH, *et al.* , 2020, HULL, *et al.* , 2020) . Still in this context, Raghu and Wilson (2020) were able to observe in their study that individuals, after hospital discharge, presented restrictive pulmonary sequelae, such as: the reduction of lung volumes and capacities, as well as diffusion alterations inherent to interstitial impairment, in addition to some important findings regarding small airway obstruction. Another consequence of SARS-Cov-2 infection on respiratory capacity is the damage generated in neural tissue by inflammatory events, causing loss of neuromuscular function, generating hypotrophy of the respiratory muscles (HADAYA;, BENHARASH, 2020; ZOUFALY, POGLITSCH, *et al.* , 2020) .

Another very important finding in post-Covid-19 individuals was also observed, is the musculoskeletal condition. In this sense, the authors Greve, Brech *et al* . (2020) will describe in their study that in the first week of hospitalization, a loss of up to 20% of quadriceps muscle mass can occur in septic individuals in the ICU. Among the main findings, the authors point out that just being in bed for a week can generate a 30% reduction in muscle strength, followed by an additional loss of 20% each following week. In view of this, it is concluded that the loss of muscle mass and strength is closely

and directly associated with deficits in the functional capacity and daily activities of these individuals (CORRÊA, KARLOH, *et al.* , 2011; NUNES, HERVÉ, *et al.* , 2020) .

Still in the scope of functional sequelae, we have that the systemic manifestations of the disease associated with the consequences, often iatrogenic, of prolonged hospitalizations and of the therapeutic measures implemented to support life, produce sequelae that not only limit exercise tolerance, but also affect the quality of life of individuals. Given this context, the objective of the present study is to present and evaluate the factors related to the persistence of symptoms in patients with post-Covid-19 syndrome after hospital discharge.

1.1.1 COVID-19

The so-called pandemic by the "Novo Corona Virus" and later named COVID-19, has its emergence dated in 2019, having only been documented and announced to the world by the World Health Organization (WHO), after the observation of several cases of infection. severe respiratory infection of unknown origin (CHENG, JIAN, *et al.* , 2020;) .

In this context, about a few days later, the identification of a virus found in an oropharyngeal *swab sample* with symptoms similar to those observed in the *Coronaviridae family occurs* , in this way, the “new coronavirus ” receives the name of SARS-CoV-2 and the disease caused by it from “ *Coronavirus disease 2019”* . Since then, it has been known as COVID-19, and later, from March 2020, the WHO would declare the pandemic by Covid-19, whose real context was already alarming, as it had more than 118,000 cases of infected people around the world. , having already caused almost 5,000 deaths (WEINBERGER, CHEN, *et al.* , 2020) .

In the practical clinical and pathophysiological context, Covid-19 can be described as a serious respiratory disease, which mainly affects the lung parenchyma and the lower airways, triggering pneumonia and SARS. The course of the disease can range from mild (81% of cases) and moderate to severe (14% of cases), requiring urgent care in an intensive care unit. The remaining 5% have critical clinical conditions combined with other multisystem complications. (MACHADO, Debora Mazioli, VIANNA, *et al.* , 2020, RAGHU, WILSON, 2020) . SULEYMAN, FADEL, *et al.* , 2020) .

1.1.2 Etiology, Pathogenesis and Epidemiology

The so-called coronavirus received this designation in 1965 due to its microscopic profile, with a structure similar to a crown, and there are seven human coronaviruses identified today, namely: HCoV-229E and HCoV-NL63, of the genus Alfacoroanavirus and HCoV-OC43. , HCov-HKU1, SARS- CoV , MERS - CoV , SARS-CoV-2, of the genus Betacoronavirus . The SARS -CoV-2 coronavirus, responsible for Covid-19, belongs to the order *Nidovirales* and the family *Coronaviridae* (DA SILVEIRA CESPEDES, DE SOUZA, 2020a, ZACHARIAH, JOHNSON, *et al.* , 2020) .

Such a virus is structurally composed of a nuclecapsid and the viral envelope, formed respectively by genomic RNA , N protein (nuclecapsid phosphorylated) and four proteins (S – *spike* , M – membrane, E – envelope, HE – hemagglutinin esterase) (TOMAZINI, MAIA, *et al.* , 2020, WIERSINGA, RHODES, *et al.* , 2020) .

Perhaps because it is a new presentation of the disease, the pathogenesis of Covid-19 is still not so clarified, however, it is understood that to enter the cell, the S protein of the viral complex tends to fix itself on the carboxypeptidase enzyme receptor correlated with angiotensin converting enzyme 2 (ACE2) (SANTOS, FINATTI, 2020, ZOUFALY, POGLITSCH, *et al.* , 2020) .

Soon after, to result in viral replication, it is necessary that the genetic material of the virus is endocytosed , and soon after fusing with the cell membrane, the RNA is converted into DNA through reverse transcription (TOMAZINI, MAIA, *et al.* , 2020) . ACE2 receptors are categorical in cardiopulmonary tissues and hematopoietic cells, and cytokine release and T cell apoptosis may occur (DA SILVEIRA CESPEDES, DE SOUZA, 2020b, PUNTMANN, CARERJ, *et al.* , 2020, WIERSINGA, RHODES, *et al.* , 2020) .

Therefore, it is suggested that in severe cases of respiratory diseases, the effect of activating a cascade coagulation occurs, due to high levels of interleukin 6 (IL-6), intense lymphopenia and great disturbance of cytokines , generating in practice an increased risk of thromboembolic events (ARENTZ, YIM, *et al.* , 2020, DA SILVEIRA CESPEDES, DE SOUZA, 2020b, MERKLER, PARIKH, *et al.* , 2020, WARE, 2020, ZOUFALY, POGLITSCH, *et al.* , 2020) .

Regarding the transmission of the virus, it was identified that this occurs via the mucous membranes of the human body, mainly through the airways, through close

contact from individual to individual, and the main means of contamination is through respiratory droplets when talking, sneezing. or coughing (CHENG, JIAN, *et al.* , 2020, DA SILVEIRA CESPEDES, DE SOUZA, 2020a) . According to the WHO, the first three days, counting from the onset of symptoms, is considered the period of greatest transmissibility, considering that the virus is mainly found in the upper airways, a place that, due to the proximity of people, increases the risk of contamination. vertical and horizontal.

However, transmission can still occur in the pre -symptomatic period, that is, between the first and third day before the onset of symptoms (TEICH, KLAJNER, *et al.* , 2020, WIERSINGA, RHODES, *et al.* , 2020) . When considering other forms of transmission, the literature says that human coronaviruses can persist viable contamination on object surfaces for up to nine days. However, these surfaces can be sanitized with 0.1% sodium hypochlorite solution and also concentrations between 62-71% of ethanol. Finally, direct contact with bodily fluids from an infected individual also becomes a major means of transmission (CHENG, JIAN, *et al.* , 2020) .

When referring to the incubation period of the SARS-CoV-2 virus, it should be noted that it can be considerably long, with an average between 5 and 6 days, with the possibility of variation from 2 to 14 days. Some authors point out that in 95% of cases, incubation occurs in 5.1 days, and 97.5% of infected individuals develop symptoms of Covid-19 around 11.5 days (MILLAR, BUSSE, *et al.* , 2020) . , PUNTMANN, CARERJ, *et al.* , 2020, WIERSINGA, RHODES, *et al.* , 2020) . Only 1%, in every ten thousand cases, develop symptoms after 14 days, and consequently, the long incubation period, the delay in the manifestation of symptoms and asymptomatic individuals, are determining factors to explain the high transmission rate of Covid-19. (GRASSELLI, TONETTI, *et al.* , 2020) .

The WHO estimated that at the beginning of the pandemic, the fatality rate could vary between 5.1% and 5.6%, which would make the SARS-CoV- 2 situation high when compared to other different types of *Influenza* . Despite the evidence that we were facing a moderate to severe pandemic, the difficulty of having a real perspective of lethality at the beginning was very great (DA SILVEIRA CESPEDES, DE SOUZA, 2020b, MILLAR, BUSSE, *et al.* , 2020) . After all, it is considered that it can be influenced by several factors such as demographic and socioeconomic conditions, mass testing capacity of the population involved, the services offered in providing diagnosis and adequate care at different levels of complexity, especially in therapy

units. intensive care unit (ICU) and health systems in each country (AMITRANO, MAGALHÃES, *et al.* , 2020, WILLIAMSON, WALKER, *et al.* , 2020) .

1.1.3 Diagnosis

Diagnosis is based on detection of viral RNA through a molecular real-time polymerase chain reaction (RT-PCR) test, which is currently considered the gold standard. This test is performed by collecting respiratory samples, such as nasopharyngeal smear or bronchial aspirate, and has high sensitivity (ability to identify individuals with the disease) and specificity (ability to identify individuals without the disease) (BÖGER, FACHI, *et al.* , 2020, DA SILVEIRA CESPEDES, DE SOUZA, 2020a, b, PUJADAS, CHAUDHRY, *et al.* , 2020, SURKOVA, NIKOLAYEVSKYY, *et al.* , 2020) . The WHO recommends that the RT-PCR test should be performed between the third and seventh day of the onset of symptoms and/or suspicion of the disease in order to obtain maximum precision in the results. However, both the long incubation time of the virus and the insufficient amount of viral genome can favor false negative results (SURKOVA, NIKOLAYEVSKYY, *et al.* , 2020) .

IgM serological tests and antibody detection are another possibility used to identify the presence of Covid-19. Both work with responses to viral infection, such as the production of IgG in affected individuals, and such tests are considered simple, fast and easy to perform, making them the best option for large groups that need a quick and low-cost response. (PALLETT, RAYMENT, *et al.* , 2020, WIERSINGA, RHODES, *et al.* , 2020 ; THE LANCET RESPIRATORY MEDICINE, 2020) . However, this test has around 30% to 40% of possibility for false negative, in addition, it is recommended to optimize the results, that individuals must present symptoms, therefore, it is not immediately recommended to be performed in asymptomatic individuals. (BATISTA, DIÓGENES, *et al.* , 2020, BÖGER, FACHI, *et al.* , 2020, DA, CHAVES, 2013, PALLETT, RAYMENT, *et al.* , 2020, TEICH, KLAJNER, *et al.* , 2020) .

For diagnostic purposes, imaging tests have been shown to be useful and differentiated, mainly to guide decision-making on therapeutic interventions. Among them, computed tomography (CT) of the chest stands out, which allows characteristic findings such as: irregular bilateral ground-glass opacity or consolidation in the peripheral areas of the lungs with septal and interlobular vascular thickening. (CHUA,

ARMSTRONG-JAMES, *et al.* , 2020, HAMMER, RAPTIS, *et al.* , 2020, POLISTINA, SIMIOLI, *et al.* , 2020, TEICH, KLAJNER, *et al.* , 2020) . Finally, although the findings change with the evolution of the disease, compatible with other forms of pneumonia, CT has not only shown good applicability and good clinical correlation, but also its fast scanning process makes it a valuable option in the diagnostic complement in patients with suspected Covid -19, and optimizes the therapeutic plan for the patient (BÖGER, FACHI, *et al.* , 2020, HAMMER, RAPTIS, *et al.* , 2020, PEGADO, SILVA-FILHO, *et al.* , 2020) .

1.1.4 Clinical condition

In Covid-19, around 80% of individuals develop mild or uncomplicated disease, 20% develop severe symptoms and will be at the mercy of treatment in an Intensive Care Unit (ICU). In the first week, symptoms are related to the spread of the virus in the body and are similar to those of common colds, in which the main symptoms include a runny nose, nasal congestion, fever, cough and sputum, and headache, tachypnea and myalgia or fatigue may also occur. (SANTOS, FINATTI, 2020 ; EL MOHEB, NAAR, *et al.* , 2020, PEGADO, SILVA-FILHO, *et al.* , 2020) .

In the next phase, usually from the seventh day, events related to the activity of the so-called inflammatory storm occur, which can change the disease status from moderate to severe. At this stage, the persistence of initial symptoms is still observed, plus broader and systemic signs and symptoms, where individuals have prolonged fever, asthenia, dyspnea, tachycardia, cyanosis, hemoptysis, hypotension and angina (GEBERHIWOT, MADATHIL, *et al.* , 2020, MERKLER, PARIKH, *et al.* , 2020, TEICH, KLAJNER, *et al.* , 2020) . In this context, in approximately 20% of cases, the presence of gastrointestinal symptoms (nausea, vomiting and diarrhea), neurological symptoms (ageusia , digeusia , stroke, ataxia, convulsions, etc.) and cutaneous manifestations (erythematous rash , urticaria) are also observed. and papillo-vesicular lesions) (EL MOHEB, NAAR, *et al.* , 2020) . In some cases, there is also a reduction in albumin levels, an increase in C-reactive protein and an increase in lactate dehydrogenase can be verified in laboratory tests, while in imaging tests, bilateral pneumonia is the main finding. (DA SILVEIRA CESPEDES, DE SOUZA, 2020a, TEICH, KLAJNER, *et al.* , 2020) . Finally, during the tenth day of the disease, individuals end up needing

hospitalization for treatment and use of supplemental oxygen therapy (IOANNOU, LOCKE, *et al.* , 2020) .

Not infrequently, some individuals who reach the most severe condition, approximately 5%, develop very uncomfortable systemic complications, conferring greater morbidity to the disease progression. According to Merkel *et al.* (2020) and Puntmann *et al* . (2020), such complications can be: severe pneumonia, progressive respiratory failure due to alveolar damage, ARDS, acute renal failure, heart failure, liver failure, sepsis and septic shock, thromboembolic events, bacterial or fungal infections , multiple organ failure , persistence of hyperthermia, decreased lymphocyte and leukocyte counts and new pulmonary infiltrates.

Taking this context into account, complications from Covid-19 usually occur in individuals who have risk factors and previous comorbidities such as: age >60 years, diabetes mellitus, arterial hypertension, smoking, obesity (BMI > 40), COPD, disease chronic kidney disease, chronic liver disease, immunodeficiency and cerebrovascular disease. So much so that, in the study by Pegado (2020), it was observed that the exacerbation of adjacent diseases and the findings of respiratory rate >30 RM and $SatO_2$ < 93%, PaO2 / FiO2 < 300, represented a poor prognosis, accompanied by a rate of mortality from SARS around 10%. Therefore, it is suggested that there is a strong association that other unfavorable pre-existing clinical conditions combined with Covid-19 significantly favor the worsening of the clinical condition, and consequently, considerably increase the mortality rate of these individuals (IOANNOU, LOCKE, *et al.* , 2020, PUJADAS, CHAUDHRY, *et al.* , 2020) .

1.1.5 Acute hypoxemic respiratory failure

Regarding the clinical and systemic manifestations of Covid-19, pneumonia can be characterized by pulmonary inflammation, where the presence of fluid in the pulmonary alveoli occurs, also being observed on CT with a predominance of alveolar changes, with up to 50% involvement. of total lung tissue (CHUA, ARMSTRONG-JAMES, *et al.* , 2020) . From a structural point of view, there is resistance in the airways and in inspiratory movements due to the accumulation of secretions, which also contributes to an increase in symptoms such as fever, dyspnea, tachypnea , cough, angina and O_2 desaturation (CHAVES, 2013).) .

The study by Araujo - Filho *et al.* (2020) suggests that, when considering imaging exams, most of the published studies highlight CT with more relevant findings, among which the main findings are: ground-glass opacity, focal consolidations accompanied by mixed opacities, among they have an inverted halo, multifocal and bilateral involvement with greater peripheral distribution, followed by predominance in the middle, lower and posterior lung fields. The author also reports that in individuals at a more advanced stage of the disease, it can be observed that the alveolar changes are superimposed by septal thickening and reticular changes, which suggests concomitant interstitial involvement. Finally, pleural effusion and incipient pulmonary fibrotic scars were also described, however, with greater evidence in the more advanced stage when compared to the initial stage of the disease (CHUA, ARMSTRONG-JAMES, *et al.* , 2020, TEICH, KLAJNER, *et al.* , 2020) .

1.1.6 Severe acute respiratory syndrome due to the evolution of COVID-19

The *Severe Acute respiratory syndrome* (SARS) or Severe Acute Respiratory Syndrome (SARS) is one of the most frequent causes of hospital admission followed by death in patients affected by Covid-19. According to the Ministry of Health, the definition of SARS is said to be an acute respiratory disease characterized by fever above 38°, cough, dyspnea, increased respiratory rate (>25 breaths/minute), and may also present with hypotension and even, gastrointestinal signs and symptoms (LANA et al. 2020).

Assuming the evolution of the disease, the clinical picture worsens as the process of acute hyperinflammation of the tissue and pulmonary edema occurs, resulting in exacerbated permeability due to the injury, and often disruption, of the alveolar capillary barrier. According to Almeida (2018), this process of pulmonary inflammation generates the release of inflammatory molecules such as cytokines , which are responsible, respectively, for the activation and recruitment of alveolar macrophages and neutrophils in the lungs, triggering the release of leukotrienes , oxidants, platelet activation and proteases. Ware (2020) explains that these substances cause damage to the capillary endothelium and alveolar epithelium, so the barriers between capillaries and air spaces are broken. As a result, the air spaces and the interstitium are flooded by edematous fluid, proteins and other cellular debris,

culminating in surfactant disruption, collapse of air spaces, misalignment between ventilation x perfusion and pulmonary hypertension (ALMEIDA, 2018, CORDIOLI, 2012).) .

Ware (2020) also describes that, in the evaluation of lung mechanics in the first 24 hours after admission to the ICU, it shows that lung compliance is decreased, along with a series of factors, suggesting a mortality of 40% to 60% in these individuals. This survival rate, evidenced in Covid-19, suggests a pathophysiology of pulmonary microvascular thrombosis due to coagulation deregulation and fibrinolysis , accompanied by lung injury, indicators of major deleterious effects in recovered individuals (CORDIOLI, 2012, REIS, LIMA, 2020, WARE, 2020) . In general, the consequences left in the body of individuals considered recovered represent persistent respiratory dysfunctions, mainly in the tissues and organs of the respiratory system, accompanied by important deficits not only directly linked to respiratory capacity during physical activities, but also, and perhaps mainly linked to BADL (basic activities of daily living), which involve basic self-care (ALMEIDA, 2018, DORNELES, 2018) .

1.1.7 Post-COVID-19 Syndrome

According to the Ministry of Health's Surveillance System, the survival rate of individuals who have experienced the most severe form of Covid-19 is approximately 50%. Although there are few published studies on the sequelae left by SARS-CoV-2 in the body, it is already known that the disease leaves traces in many systems (LANA et al. 2020). In the study by Juárez-Belaúnde , Colorme font *et al* . (2020), in their report to the journal of Neurologia, states that the pathophysiological process of the disease comes from an inflammatory response that mainly affects the respiratory system. However, the author emphasizes that new studies have been identifying sequelae of great significance, also in the cardiovascular, neurological and musculoskeletal systems. As described by the WHO, the probability of deficits in these systems increases in individuals who have undergone periods of ICU stay, combined with the need to use respirators. As a result, the morbidities acquired in the process leave important impacts on the functional and cognitive capacities of recovered individuals (GREVE, BRECH, *et al.* , 2020, PAHO/WHO, 2020) .

1.1.8 respiratory disorders

fibrotic normalities , previously associated with the idiopathic cause, are the main consequences left by the passage of Covid-19, so that its manifestations can result from any stage, being evidenced more frequently in cases that have undergone the most severe form of the disease. illness. Consequently, the lung damage caused by SARS-CoV-2 infection in the acute phase results from the combination of some expected clinical manifestations, such as: edema formation, alveolar release of epithelial cells and deposition of hyaline material in alveolar membranes . POGLITSCH, *et al.* , 2020) . During the 2nd and 4th weeks, the lungs show signs of fibrosis, characterizing the next phase of the infection, where fibrin deposition occurs, infiltration of inflammatory cells and fibroblasts adjacent to the epithelial cells in the alveolar spaces (HULL, LLOYD, *et al.* , 2020) .

A little further on, during the 6th to 8th week, the lung tissue becomes fibrotic , in addition, bilateral lesions tend to be observed. In this context, Raghu and Wilson (2020) observed in their study that individuals, after hospital discharge, present restrictive abnormalities such as reduced diffusion capacity and small airway obstruction. Some authors also suggest that these abnormalities may be common in lung function, especially in individuals who have reached the most severe form of Covid-19, due to high inflammatory rates and pulmonary fibrosis.

Despite what is already evidence on the multisystem sequelae of Covid-19, several other studies are emerging around the sequelae left in the respiratory system after infection by the SARS-CoV-2 Coronavirus , suggesting that these may vary in individuals who have had it. mild, moderate or severe frames. The same authors also state that the resolution of the abnormalities may occur within the next 6 to 12 months after the infection, or even become permanent (HADAYA, BENHARASH, 2020) .

Another consequence of SARS-Cov-2 infection on respiratory capacity is the damage generated in neural tissue by inflammatory events. This in turn receives information from mechanoreceptors and chemoreceptors in the lungs and/or provides innervation to organs, airway smooth muscle, glands and vasculature . Strike, Brech *et al.* (2020) report in their study that some complications and/or deficits left in respiratory capacity may be the result of cardiorespiratory arrest after damage to the innervations of the heart, lungs and other organs of the cardiorespiratory system, as well as loss of neuromuscular function and muscle trophism . . Thus, it can be considered that decreased cardiorespiratory function, decreased inspiratory muscle strength and, consequently, functional capacity are linked to the worsening of

symptoms resulting from SARS-Cov-2 infection in neural tissue linked to organs and/or structures in the system. respiratory system (HADAYA;, BENHARASH, 2020, ZOUFALY, POGLITSCH, *et al.* , 2020) .

1.1.8.1 Neurological Dysfunctions

There are some hypotheses and speculations about the way in which the virus accesses the nervous system, the main one being the one that defends the idea that one of the transsynaptic pathways of the vagus nerve would be responsible (INCIARDI, LUPI, *et al.* , 2020) . , LU, LI, *et al.* , 2020) . This hypothesis is due to the fact that its innervation involves the lower part of the airways through the nasal and olfactory epithelium (GREVE, 2020; WEI, LIU, *et al.* , 2020) . But there are differences between the authors, so much so that some still discuss a second hypothesis, which the spread would occur via hematogenous , with the virus crossing the blood -brain barrier . (MATSCHKE, LÜTGEHETMANN, *et al.* , 2020) . However, when observing the neural tissue infected by SARS-CoV-2, the induction of cellular apoptosis by the virus was observed, where the mechanisms of apoptosis are similar to those of demyelinating diseases , which I could give more support to the first hypothesis (JUÁREZ-BELAÚNDE , COLOMER FONT, *et al.* , 2020, MATSCHKE, LÜTGEHETMANN, *et al.* , 2020) .

Taking into account individuals hospitalized due to severe Covid-19 infection, they may be susceptible to central and peripheral nervous system injuries, so that their inherent neurological sequelae are not limited to functional damage only, but complications such as confusional syndromes , vascular accident. cerebral palsy (CVA), encephalopathies, encephalitis, polyneuropathy and Guillan -Barre syndrome , confirming a significant functional impact and also quality of life (INCIARDI, LUPI, *et al.* , 2020, JUÁREZ-BELAÚNDE, COLOMER FONT, *et al.* , 2020) .

Among the main neurological complications, it was observed that about 20% of individuals affected by Covid-19 had among the main signs and symptoms, namely: changes in consciousness, seizures or epileptic status, paralysis, CVA (cerebrovascular accident), infectious neuropathy, peripheral polyneuropathy , in addition to possible necrotizing myopathy (LU, LI, *et al.* , 2020, SHAHJOUEI, NADERI, *et al.* , 2020) . However, the author considers it pertinent to note that the so-called critically ill polyneuropathy , in general an infectious mixed sensorimotor neuropathy,

by itself already causes axonal degeneration , and necrotizing myopathy , in turn, can cause fatty degeneration, hypotrophy and fibrosis. Such conditions are frequently observed, respectively, in 46% and 48% to 96% of individuals who experience prolonged ICU stay (GREVE, BRECH, *et al.* , 2020) .

1.1.8.2 musculoskeletal disorders

As is widely known, the condition of physical inactivity, caused by hospitalization in the ICU (or even social isolation), can significantly impact the muscle homeostasis of individuals. In this context, the inflammatory process caused by Covid-19 infection promotes musculoskeletal consequences that are often catastrophic, impacting and can last for a long period of patients' lives, drastically reducing their quality of life. This condition seems to be more evident in individuals who remain in hospital for long periods, however, the author explains that this process involves several conditions to which individuals are exposed, such as the inflammatory process, immobility, in addition to insufficient nutritional and caloric support, apart from The administration of corticosteroids is often carried out without such criteria, given the complex contexts in which patients are inserted (GREVE, BRECH, *et al.* , 2020) .

Even before the Covid-19 pandemic, it was already widely known that patients who are exposed or subjected to long periods of immobility, precisely due to the absence of exposure to mechanical discharges, end up triggering an adaptive response, which, among other things, includes: of protein synthesis, increased degradation and apoptosis of muscle cells (sarcomeres), leading to the dreaded sarcopenia. When such a condition sets in, there is inevitably a loss of homeostasis in the renewal of muscle tissue, accelerating the process of hypotrophy and loss of muscle strength (NUNES, HERVÉ, *et al.* , 2020) .

Strike, Brech *et al* . (2020) also describe in their study that in the first week of hospitalization, a loss of up to 20% of thigh muscle mass can already occur in septic individuals in the ICU. The author also points out that one week in bed can generate a 30% reduction in muscle strength, followed by an additional 20% loss each following week. In view of this, it is concluded that the loss of muscle mass and strength will directly impact the physical capacity or even daily activities of these individuals, generating a significant negative impact on the quality of life of patients affected by

Covid-19, and who have experienced such a situation (CORRÊA , KARLOH, *et al.* , 2011, NUNES, HERVÉ, *et al.* , 2020) .

1.1.9 Persistence of symptoms in Post-COVID-19 Syndrome

1.1.9.1 dyspnea

The dyspnea symptom, popularly known as shortness of breath, can be characterized as a form of subjective experience of uncomfortable breathing, consisting of qualitatively distinct sensations that may vary in intensity, and may also present a range of symptoms not only with multiple interactions of physiological origin. , but also with multidimensional factors, such as psychological, social and environmental, often culminating in the situation described by some authors as " total dyspnea " (MARTINEZ et al., 2004). However, expressions such as difficulty, effort, weight or discomfort to be able to breathe, sensation of shortness of breath, or hunger for air, feeling of oppression or tightness in the chest, are also widely used by patients in an attempt to describe the dyspnea symptom (ZIEGLER, 2011) .

Some specific literature data show that dyspnea is usually present in up to 20% of the general population, being directly associated with increased morbidity and mortality, also generating limitations in physical and social activities and in the quality of life of individuals, especially when related to problems cardiac, pulmonary or even neuromuscular disorders, often within a hospital setting or even prolonged hospitalization (IOANNOU, LOCKE, *et al.* , 2020, NUNES, HERVÉ, *et al.* , 2020) .

In this context, it is common for individuals with cardiopulmonary complications to report dyspnea while performing physical activities, which can range from the mildest to the most strenuous, depending on the degree of punctual or systemic involvement involved (BOHN JÚNIOR, COSTA, *et al.* , 2020) . There are some plausible explanations found in the literature, based on the premise that during physical activities, there is greater consumption of oxygen and, consequently, greater production of CO_2 (carbon dioxide) (BOHN JÚNIOR, COSTA, *et al.* , 2020, CORRÊA , KARLOH, *et al.* , 2011)

Other authors also suggest that, in response to the detection of high concentrations of CO_2 and low concentrations of Oxygen, the bulbar respiratory center increases the respiratory rate as a way of compensating for homeostatic maintenance. In normal situations, this process does not generate discomfort, on the other hand, in the case of pathological contexts, where there is a deficit in cardiac or pulmonary functions, the respiratory rate and shortness of breath can be increased even in rest situations (DORNELES, 2018). ; SOUZA, VIEIRA et al., 2020) .

Not infrequently, there may be situations in which dyspnea can cause so much discomfort that individuals feel incapable of breathing with adequate depth and speed due to exacerbated ventilatory demand, and it is quite common for them to frequently report the perception that chest expansion when breathing in this difficult and reduced, as well as expiration (which should be a practically passive process) demands greater efforts than normal (SIMSIC, 2016) .

As an inevitable consequence, the increase in Respiratory Frequency (RR), together with shortness of breath, considerably affect the performance of physical and daily activities of individuals, generating a significant functional impact and directly implying in the reduction of the quality of life of the individuals involved (BOHN JÚNIOR, COSTA, *et al.* , 2020, ZIEGLER, 2011) .

1.1.9.2 Dyspnea assessment

As already mentioned, dyspnea can be defined as a subjective perception of increased work of breathing, which generates a distressing sensation of shortness of breath, perceived as inadequate ventilation. Therefore, dyspnea, triggered when performing activities of effort, seems to be one of the most frequent complaints and tends to be more frequent among individuals who have impaired lung function, especially in the post-covid-19 period (O'DONNELL *et al . al* ., 2007).

The sensation of dyspnea in certain individuals during exertion leads to a progressive reduction in physical activity, and this condition can generate a vicious cycle, affecting not only the functional state and physical conditioning, but also the performance of their activities of daily living, having an impact. directly on the patient's quality of life (TROOSTERS *et al.,* 2005).

In this context, the literature provides a significant amount of instruments and scales to assess the degree of dyspnea in these individuals, whether through

subjective assessment, limitation of activities of daily living or functional disability (CABRAL, LOPES, *et al.* , 2017, PISSULIN, PACAGNELLI, *et al.* , 2018) .

Therefore, we can consider that among the unidimensional scales, the multidimensional instruments, the most used in practice are: the visual analogue scale (VAS), the Borg scale, the modified scale of the British Medical Research Council (MRC), basal index of dyspnea (BDI), transitional dyspnea index (BTI), in addition to the *PFSDQ* (pulmonary functional status and dyspnea questionnaire) (VELLOSO, COSTA, OZEKI, 2002)

The Visual Analog Scale (EVA), created by Scott Co. Laboratory , in 1920, has been used to measure different subjective aspects such as mood, pain, anxiety and dyspnea , and since then it has been widely used in clinical practice to measure dyspnea both at rest and during exercise (AITKENS, 1969).

We have the modified Borg scale , which is characterized by being a subjective scale, adapted by BURDON, in 1982, to measure dyspnea both during exercise or in physical activities, since the measurement is made directly at the moment of that the patient is experiencing the sensation (BORG, 1998). The Borg scale seeks to assess the subjective sensation of exertion (also described as a sensation of respiratory fatigue), and covers a score from 0 to 10, where: 0 means no respiratory difficulty, while 10 represents maximum respiratory difficulty.

Because it is an extremely subjective scale, over time, and in order to allow a better understanding of the perceived exertion by the evaluated individual, the insertion of quantitative expressions of intensity was established so that there was a direct correlation between the numerical categories. and verbal descriptors (HIGBEE, DODD, 2020, SILVA, DIAS, *et al.* , 2011) . It is worth mentioning that the Borg scale includes instructions for its use, together with the structure to be evaluated, seeking not only to facilitate the individual's understanding, but above all to increase the accuracy of the response in relation to the subjective perception of effort during the proposed activities (CABRAL , LOPES, *et al.* , 2017, GOMES, SHUJMANN, *et al.* , 2019, LIMA DE, MAGALHÃES, *et al.* , 2019) .

The assessment of dyspnea in relation to limitations in performing routine activities requires some intersection between uni and multidimensionality, so that it is possible to quantify it. In this context, the most cited scale in the literature is the Modified Scale of the British Medical Research Council (*MMRC - Modified Medical Research Council*), created by English pulmonologists in 1960, and since then it has

been used to measure breathing difficulty in ADLs (activities of daily living) and perceived respiratory incapacity (BESTALL *et al* ., 1999, DA CAPITAL et al. , 2018).

MMRC scale is composed of only five items, with the patient choosing the item that corresponds to how much dyspnea limits their ADL, indicating their subjective degree of dyspnea by choosing a value between 1 and 5: 1 (only suffers from lack of breath during strenuous exercise), 2 (suffers from shortness of breath when walking quickly or walking up a gentle slope), 3 (walks slower than people of the same age because of shortness of breath or has to stop for breath even when walking slowly), 4 (breathing pause after walking less than 100 m or after a few minutes) and 5 (feeling so short of breath that you no longer leave the house, or feel short of breath when getting dressed) (KOVELIS, DEMETRIA *et al* . , 2008).

In practice, the MMRC scale is an instrument of easy applicability, understanding by the patient and reproducibility by the examiner, and consists of the correlated and adjective description of dyspnea during daily activities, which often fit the reality of individuals with breathing difficulties in basic activities. , how to leave the house, or even when dressing (CAMARGO, PEREIRA, 2010, KOVELIS, SEGRETTI, *et al.* , 2008, ZIEGLER, 2011; PISSULIN, PACAGNELLI, *et al.* , 2018) .

Regarding the multidimensional instruments for dyspnea assessment, we have the Basal Dyspnea Index (BDI) (developed by MAHLER *et al* ., 1984) has been used to assess and measure the direct and indirect impact caused by dyspnea on individuals' lives, being divided into three distinct domains, however, correlating the magnitudes: functional disability, tasks and effort, facilitating a more detailed and multidimensional assessment of the impact of dyspnea on each individual's life. The BDI also has some specific characteristics, as it correlates a grade from 0 to 4 for each aforementioned domain, in addition to a field that includes, in addition to the subjectivity of the symptom, it also allows the association of the dyspnea symptom with other physical, emotional or behavioral aspects.

Regarding the use of multidimensional questionnaires for direct and correlated assessment of dyspnea, in the international literature, the following stand out: The - *Pulmonary* Questionnaire *Functional Status and dyspnea Questionnaire - Modified version* (PFSDQ- M), in its translated, adapted and validated version for Portuguese. For clarification and specification purposes, we have that PFSDQ-M (Modified version of *Pulmonary Functional Status and dyspnea Questionnaire*) is composed of three domains: influence of dyspnea on ADL, influence of fatigue on ADL (5 general and 10

specific items for each domain) and change in ADL compared to the period prior to the disease (10 specific items). With regard to these domains, the patient is instructed to indicate how much dyspnea and fatigue interfere with the 10 specific ADL items, - choosing a value between 0 and 10 for each activity, with the respective meanings: 0 (no interference), 1-3 (mild), 4-6 (moderate), 7-9 (severe) and 10 (very severe). In the third domain, the patient reports the impact on the change in ADL compared to the period before the disease, choosing for each activity a value between 0 and 10: 0 (as active as always in relation to this activity), 1 -3 (small change), 4-6 (moderate change), 7-9 (extreme change) and 10 (no longer do this activity) (KOVELIS, DEMETRIA *et al,* 2008).

After this personal and non-transferable stratification by the patient, not only is a partial score calculated , ranging from 0 to 100 for each of the three domains (dyspnea , fatigue and change in ADL), and a total score is formed by the sum of the partial scores of the three domains, totaling a value that varies from 0 to 300. It is worth mentioning that there are five general questions in the dyspnea and fatigue domains that are merely informative and qualitative, and their answers are not counted in the questionnaire score . For purposes of interpretation, higher values on the scale indicate greater limitation in ADL (LAREAU, MEEK, ROOS, 1998).

1.1.9.3 Musculoskeletal Change in COVID-19

Excessive production of pro-inflammatory cytokines in hypercatabolic conditions is associated with oxidative stress , which promotes the production of corrosive molecules that cause severe damage to myocytes (WELSCH C *et al* ., 2020). The exact dynamics underlying muscle wasting in COVID-19 are still unclear. However, the researchers suggest that muscle loss in COVID-19 patients is a result of a wide range of interrelated factors (Figure 1).

Aging, as well as metabolic and inflammatory disorders (diabetes, obesity, cardiovascular disease, cancer, etc.), are associated with baseline states of protein-energy malnutrition and hyperinflammatory systemic diseases that contribute to peripheral muscle dysfunction (PMD). In the context of COVID-19, these individuals are usually also the majority of affected patients and thus have ample possibilities of peripheral muscle dysfunction. Undoubtedly, elderly people affected by SARS-CoV-2,

especially the severe forms, are likely to express dramatic injuries to their muscle structure, especially in the late stages of the disease (PITSCHEIDER, L *et al.,* 2020; JIN M *et al. ,* 2020).

The exact musculoskeletal consequences for patients with COVID-19 have not yet been fully established. Although the respiratory tract appears to be the primary site of infection, compromised alveolar epithelium in some COVID -19 patients can lead to the development of viremia , and cells in other tissues may be susceptible to direct viral infection *. al.,* 2020; DISSER *et al.,* 2020) .

In addition to the potential direct viral infection, infection -induced proinflammatory cytokines and signaling molecules can lead to pathological changes in skeletal muscle tissue. C-reactive protein (CRP) is a biomarker commonly used to assess inflammatory processes in general, and current studies have shown that critically ill patients with COVID-19 have much higher CRP levels than healthy individuals. Several of the pro-inflammatory signaling molecules known to be elevated in COVID-19 patients can also affect musculoskeletal tissue (DISSER *et al.* , 2020) .

Patients who needed to be admitted to an intensive care unit (ICU) or stayed in the hospital for long periods tend to have more musculoskeletal complications that require rehabilitation. The period of hospitalization is directly related to longer periods of hypomobility and/or immobility, resulting in fatigue, muscle weakness and polyneuropathy . (BARKER-DAVIES *et al* ., 2020; FELIPPE FELIX MEDIANO *et al* ., 2020) .

Myalgias and generalized weakness have been reported in symptomatic patients with COVID-19. Although some data have suggested that the occurrence of muscle pain does not increase with the severity of COVID-19, in patients with computed tomography (CT) or radiographic imaging of the abnormal lungs, myalgias were an important predictor of overall disease severity (DISSER, et al., 2020) .

Even after hospital discharge, some patients report difficulties in activities of daily living (ADL), such as walking and climbing stairs. This suggests that SARS infection leads to deficits in both muscle strength and endurance, probably due to the pro-inflammatory effects of the viral infection and the deconditioning that occurs during the period of convalescence. The reduction in the functional capacity and physical fitness of these patients corresponded to falls in several health-related quality of life indices (DISSER *et al,* , 2020; LAU *et al* , 2005) .

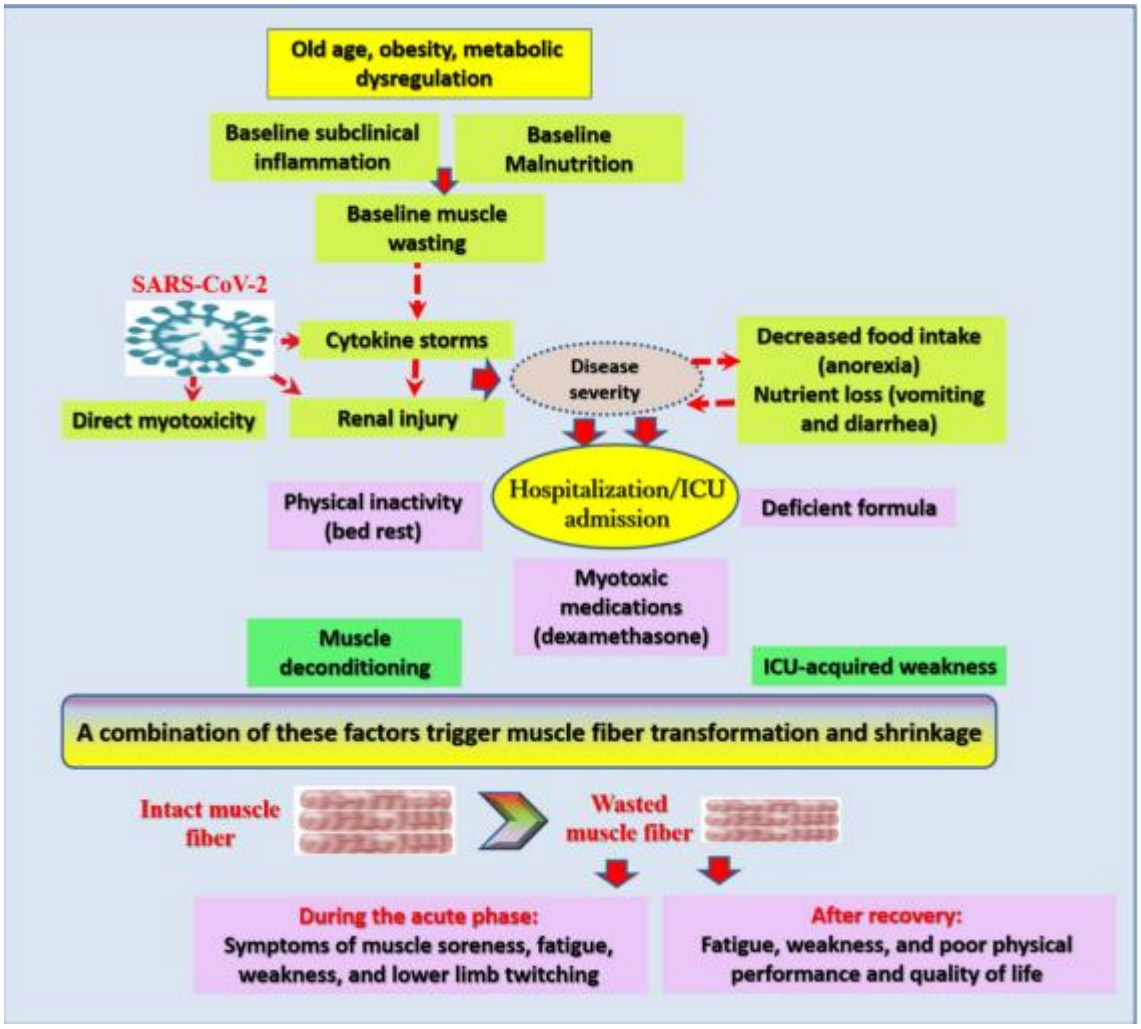

Figure 1: Pathophysiological hypothesis for peripheral muscle dysfunction in COVID-19. (Source: MOHAMED ALI A & HIROSHI K, 2020)

1.1.9.4 Peripheral muscle assessment

As previously discussed, peripheral muscle dysfunction has a substantial contribution to peripheral muscle fatigue. The impact of this dysfunction on muscle performance is developed by abnormalities in muscle structure, bioenergetics and function. Some important clinical implications are related to changes in muscle structure (mass) and function (strength and endurance), such as reduced exercise capacity, quality of life, and survival in several pulmonary conditions, including COPD, which we could similarly to assume similar changes in the dysfunctions induced by COVID-19. The etiology of these abnormalities appears to be multifactorial, involving factors such as deconditioning , hypoxia and/or hypercapnia , oxidative stress , senescence, hormonal dysfunction, systemic inflammation, chronic or repetitive use of drugs (corticosteroids) and nutritional depletion.

The involvement of inflammatory mediators in PMD is suggested by the observation that systemic inflammatory markers are related to poor contractile muscle performance in several pulmonary conditions such as COPD, ASTHMA and interstitial lung diseases (RONDELLI RR *et al.,* 2009) . For example, quadriceps strength was negatively associated with IL-8 levels during exacerbation of lung diseases (SPRUIT MA *et al.,* 2003) and with IL-6 and TNF-α levels in the elderly (YENDE S *et al.,* 2006). In very critically ill patients, high CRP levels were associated with reduced strength, endurance and quality of life. On the other hand, in another study, it was evidenced that the marked weakness of the quadriceps was significantly related to the average daily dose of steroids used by the patients during the acute exacerbation of pulmonary diseases. The deleterious effects of steroids on skeletal muscle function have been attributed to the inhibition of protein synthesis and increased protein degradation. Other evidence suggests the role of oxidative stress in muscle dysfunction in hyperinflammatory lung diseases . COVID-19 is known to cause an inflammatory, multisystemic storm implicated over time in several peripheral dysfunctions, including muscle dysfunction. All determinants of muscle dysfunction in pulmonary diseases are summarized in Table 1.

determinant trigger	Abnormalities	dysfunction
hyperinflammatory stress	↑↑ pro-inflammatory cytokines such as IL1, TNF-alpha, IL-8, IL-6	↓muscle performance
Use of corticosteroids	↓protein synthesis and ↑muscle catabolism	↓muscle performance during exercise, worsening dyspnea and fatigue
Acute and/or chronic hypoxemia	↑inflammatory mediators, ↓ATP and muscle glycogen	↓muscular strength and endurance , ↓muscle performance but activities of daily living.
oxidative stress	Oxidant and anti-oxidant imbalance	↓muscular endurance
Immobility and sedative and neuromuscular blocking agents	↓type I fibers and ↓oxidative enzymes ↑IIx fibers (hypotrophied)	↓muscular endurance and muscular ↓performance during exercise

Table 1: Metabolic and bioenergetic determinants of peripheral muscle fatigue in lung disorders and their consequences. (Modified from: RONDELLI RR *et al.,* 2009)

Currently, there is a wide variety of models, tests and exercise protocols being used, aiming to obtain parameters indicative of muscle fatigue in patients with COPD (Vøllestad NK *et al.,* 1997).

Functional assessment methods of peripheral muscle fatigue basically involve three basic components:

I) the muscle activation strategy: voluntary effort or exogenous stimulation

II) the condition of the exercise (isometric, isoinertial or isokinetic)

III) the exercise pattern: time and intensity, which may involve a single prolonged contraction or a series of repeated contractions

Most of the methods used in this evaluation in patients with pulmonary or cardiac diseases preferentially focus on the muscles of the lower limbs. It should be noted, however, that the function of the upper limbs remains relatively preserved in these patients.

maximum voluntary contraction

The assessment of muscle strength and endurance can be obtained by maximal voluntary contraction (MVC). This assessment can be done by instructing the patient to generate as much voluntary force as possible without altering muscle length (symmetrical test) or by encouraging the patient to perform a full range of motion with the greatest possible load (1RM test). In this evaluation, equipment such as tensiometers or dynamometers can be used to quantify the generated isometric force (if there is no change in muscle length). In the case of the 1 RM test, the highest load imposed and that the patient can complete and repeat is considered. As these are volitional techniques, external complicating factors, such as the patient's functional ability and motivation, can generate submaximal contractions and thus underestimate the analysis. However, due to the ease of execution, verbal encouragement and technical experience, little variability has been described in our tests involving maximal voluntary contraction (MVC). In patients with chronic pulmonary dysfunction, the loss of the ability to generate or maintain MVC during knee extension exercise has been representative of muscle fatigue. (SWALLOW EB *et al.,* 2007). Studies have used series of submaximal voluntary contractions in the evaluation of resistance and peripheral muscle fatigue. Usually, relative values of approximately 20-60% of MVC (1RM test or isometrically sustained maximal voluntary contraction) are required to be sustained until exhaustion, maintaining cadence and rhythm constant or close to it. Resistance is measured by the time the task is maintained. The test should be stopped

when there is a failure to maintain the intensity of the contraction (5% drop) or inability to complete the range of motion or visually there are signs of muscle fatigue, such as fasciculations , for example.

1.1.9.5 Fatigue

Within the spectrum of most common symptoms in post-COVID-19 patients, non-specific chronic pain, cough, dyspnea, myalgia, arthralgia , and fatigue stand out (AZUMA *et al.,* 2020). However, it is worth mentioning that in any chronic post-viral syndrome, it can present with a feeling of fatigue and lack of energy, in addition to nonspecific myalgia, which can also generate depression and even sleep disorders, as shown by the various characterizations of post-infection by the virus. SARS-CoV-2. Such long-term adverse effects, which are extremely similar to those experienced by patients with chronic fatigue syndrome (CFS) and fibromyalgia syndrome, indicate a significant burden of these ongoing symptoms in patients with COVID-19 (MOLDOFSKY *et al.,* 2011; MANDAL *et al., 2011; MANDAL et al. al.,* 2020).

Classically, muscle fatigue is conceptualized as the muscle's inability to generate or maintain levels of force required for a given rate of work (VØLLESTAD NK, 1997). Muscle fatigue can be divided into two components: central and peripheral. This terminology is given by the anatomofunctional sites involved in the fatigue process. In central fatigue, muscle activation from the central nervous system is compromised, whereas in peripheral or contractile fatigue, involvement is distal to the neuromuscular junction. Figure 2 shows a representative illustration of the structures involved in central and peripheral fatigue.

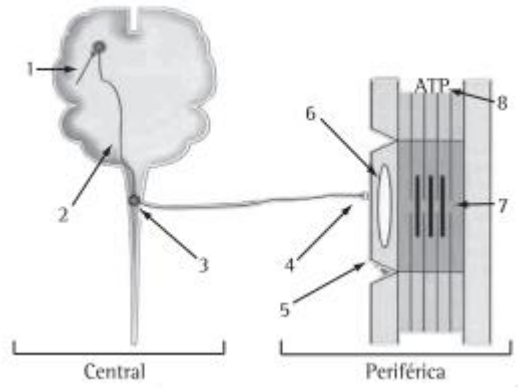

Figure 2: The main potential sites of muscle fatigue: Central fatigue relates to changes in (1) the excitatory command to the upper motor centers or (2) the lower motor neuron and (3) its degree of excitability, or (4) the transmission neuromuscular. Peripheral fatigue occurs when the alterations are related (5) to the excitability of the sarcolemma , or (6) to the release and reuptake of calcium by the T tubules and the sarcoplasmic reticulum, or (7) to contractile mechanisms, or even (8) to the supply of energy and/or accumulation of metabolites. (Source: RONDELLI RR et al., 2009)

Most often described as a manifestation of tiredness, lack of energy or exhaustion associated with impairment in the performance of usual day-to-day activities, the current definition of fatigue describes it as a symptom resulting from an underlying pathophysiology or resulting from a specific treatment. performed, then fatigue is understood as a sequel, which proves to be refractory to the usual energy recovery strategies. The fatigue symptom is very prevalent in clinical situations such as oncological diseases, heart failure, fibromyalgia and chronic obstructive pulmonary disease, in addition to conditions related to the frailty of the elderly (MOTA *et al.,* 2005; WINTER & FOWLER, 2009).

In this context, a recent study found that while the symptom burden in individuals recovering from hospital admission with COVID-19 generally improved at initial follow-up, 53% reported persistent shortness of breath, 34% persistent cough, and 69% persistent fatigue (MANDAL *et al.,* 2020). already Perrin *et al.* (2020) described these persistent symptoms as fatigue, diffuse myalgia, depressive symptoms and sleep disturbances comprising a broad spectrum called post-COVID-19 syndrome (PERRIN *et al.,* 2020).

In a recent review of the pathophysiological mechanisms of chronic fatigue in post-COVID-19 patients, the authors defend the premise that post-COVID-19 fatigue syndrome may result from damage to olfactory sensory neurons, causing an increase in resistance to flow. of cerebrospinal fluid (CSF), and further leading to congestion of

the lymphatic system with subsequent toxic accumulation. within the central nervous system (CNS) which could biologically explain the persistence of this symptom. The lymphatic system, described in recent works as a perivascular network, where a large proportion of subarachnoid cerebrospinal fluid circulates , responsible for the drainage of toxic residues from brain metabolism. This whole-brain pathway has been called the “lymphatic system”, based on its similarity in function to the peripheral lymphatic system, and its functions have been described in the pathophysiological scope of Alzheimer's Disease (JESSEN *et al.,* 2015).

Taking into account some clinical findings in practice, it has been suggested that chronic fatigue syndrome would be associated with idiopathic intracranial hypertension without pathologically elevated intracranial pressure, some authors have argued that chronic fatigue syndrome could have a clear neurophysiological explanation based on obstruction. of the lymphatic system (WOSTYN P, 2021).

Among other biological hypotheses, it is assumed that post-viral infection fatigue syndrome is based on the inflammatory storm that COVID-19 as well as other syndromes previously presented. Furthermore, fatigue has been associated with infections, which often occur outside of an epidemic or pandemic scale, results that are not limited to just viral infections, but also bacterial infections (HICKIE *et al.,* 2006; MOLDOFSKY *et al. ,* 2011).

Given this evidence, it was expected that some COVID-19 survivors would develop post-infectious fatigue, based on the hypothesis that the inflammatory storm caused by SARS-COV-2 infection may, by association with the findings already described in severe viral infections, explain the persistent and prolonged fatigue in the post-covid-19 (JOHNSON *et al.,* 2020).

1.1.9.6 Fatigue Assessment

The term fatigue is defined as " extreme tiredness resulting from mental or physical exertion or illness " and is also used to describe a nonspecific but debilitating symptom in a range of chronic diseases such as cancer, multiple sclerosis, stroke, and depression. The subjective nature and severity of fatigue are assessed using psychometric tools, such as self -report questionnaires and scales (ELBERS *et al.,* 2008; WHITEHEAD L, 2009; KRUPP *et al.,* 2010; MITCHELL SA, 2010).

The relative merit of objective and subjective measures of fatigue is dependent on the clinical situation in which it is intended to be studied. For example, in a clinical population where fatigue can be chronic and have a devastating impact on quality of life (QOL) and/or physical function, specific instruments are multidimensional or not clearly justified.

In a last Brazilian consensus document, fatigue is defined as a subjective and persistent feeling of tiredness, physical, emotional and/or cognitive exhaustion, disproportionate to recent activity, which does not improve with rest and sleep and which interferes with activities of daily living (DE FADIGA, 2010).

Twenty-one instruments validated worldwide for fatigue assessment are described in the literature (Chart 2). In Brazil, there are 7 cross- culturally validated fatigue instruments (Chart 3).

FATIGUE ASSESSMENT INSTRUMENTS WORLDWIDE
Fatigue Severity scale
visual analogue scale for fatigue
Fatigue Assessment instrument
Brief mental fatigue Questionnaire
Chalder Fatigue Scale
Fatigue Impact scale
Multidimensional Fatigue Inventory
Fatigue Symptom inventory
Dutch Fatigue Scale
Dutch Exertion Fatigue Scale
Piper Fatigue Scale
Revised-Piper Fatigue Scale
Schwartz Cancer Fatigue Scale
Brief Fatigue Inventory
Cancer Fatigue Scale
Schedule of Fatigue and Anergia for Chronic fatigue Syndrome
Schedule of Fatigue and Anergia for General Practice
Cancer-related Fatigue Distress Scale
Fatigue Impact Scale for Daily Administration
Fatigue Pictogram
Fatigue Symptom Check list

Table 2: International instruments for fatigue assessment (Modified from: Brazilian Consensus on Fatigue, 2010).

In this context, and in the face of so many instruments and scales available, based on the experience of specialists and available knowledge, the Brazilian Consensus on Fatigue (2010) suggests a flowchart for an adequate assessment of the fatigue symptom, as follows: at the time of diagnosis, the realization of three sequential questions. Once the presence of the fatigue symptom is identified, an initial assessment is carried out to quantify the symptom, using a numerical scale (score between 0 and 10;), the Fatigue Pictogram (MOTA, PIMENTA, FITCH, 2009). Having the interest and condition of making a more detailed assessment of the symptom, including seeking to know the dimensions of fatigue, we suggest the use of a multidimensional scale such as the Piper Fatigue Scale-Revised (MOTA, PIMENTA, PIPER, 2009) . After the initial evaluation of the symptom, one should investigate the causes of fatigue, mitigating and exacerbating factors, implement the treatment and periodically reassess the presence and intensity of the symptom (DE FADIGA, 2010). (Instruments and scales mentioned in the annex)

FATIGUE ASSESSMENT INSTRUMENTS VALIDATED IN BRAZIL(*)
Fatigue Severity Scale
Chalder Fatigue Scale
Fatigue Impact Scale
Dutch Fatigue Scale
Modified Dutch Fatigue Scale
Piper's Revised Fatigue Scale
Picogram of Fatigue

Table 3: Instruments validated in Brazil for fatigue assessment *Modified from: Brazilian Consensus on Fatigue, 2010.

1.2 Pilates Method

Pilates has become one of today's buzzwords thanks to the influence of media and social media. Hundreds of new exercise videos added to the internet every day, including elite athletes and famous people, have made the pilates method (MP) even more popular (THOMPSON WR, 2017). Pilates is not an exercise approach that includes predetermined standard positions and movements, on the contrary, it is a training method that anyone can do that increases physical strength, flexibility and

coordination, balance, reduces stress and anxiety, improves well-being and mental focus (UNGARO A, 2011). The basic principle of the Pilates method is the technique of centering the body and mind based on providing and maintaining stability (ADAMS M *et al.,* 2012).

Pilates , which was introduced in the context of rehabilitation by medical units dealing with dance, has been the exercise-based method of choice in the dance and fitness world for a long time. Training based on the precepts of Pilates is used as part of rehabilitation programs for musculoskeletal disorders and patients with neurological disorders, postpartum, chronic pain, arthritis and many other movement disorders. It is also preferable in special groups such as children and the elderly, as well as in adults, for the protection and improvement of general health (BYRNES K *et al.,* 2018).

History of Pilates

Joseph Hubertus Pilates , the founder of the Pilates concept , was born in 1880 in Düsseldorf, Germany. His childhood was spent with illnesses such as asthma and rickets. He majored in gymnastics, boxing, yoga and karate to improve his health. He was a circus performer, and self-defense instructor as a young man. Combining Eastern and Western philosophies, he began to develop his own system of exercises called *Contrology* . His method soon gained popularity in Germany. He immigrated to the United States in 1926 and quickly became popular while continuing his studies (OWSLEY A, 2005). Joseph Pilates died in 1967 at age 87. Since his death, his work has been continued by many students (LATEY P, 2001; WOOD S, 2018). The principles outlined by Joseph Pilates in his book *Return to Life through Contrology* are still valid today, and there are two more principles in modified forms of Pilates training . These eight principles previously described and adopted today in the context of musculoskeletal rehabilitation are: concentration, control, centering, fluency, precision, breathing, relaxation and resistance (WOOD S, 2018).

Pilates training principles

Concentration : Pilates training requires a mental focus on the target area of the body itself. Concentration draws attention to the working body segment, potentially improving functioning and, ultimately, improving the quality of movement (MUSCOLINO JE *et al.,* 2004).

Control : Pilates training is aimed at contracting the right muscle at the right time so that proper movement can take place. Each stage from start to finish of the movement continues and ends under control. Controlled movement also reduces the risk of injury (IULIAN-DORU T *et al.,* 2013).

Centering : There are many muscles in the abdomen, lumbar region and hip complex, which is accepted as the center of our body and called the central region. Muscles such as the multifidus , quadratus lumborum, iliopsoas , transversus abdominis, and diaphragm in this are primarily involved in protecting the lower back. One
strong and active core is an indication of a strong center. With centralization, movements of the head, shoulders, chest, pelvis and extremities are organized around a central base (MUSCOLINO JE *et al.,* 2004; IULIAN-DORU T *et al.,* 2013).

Fluency : In Pilates training , the flow of movements is continued with a mind-body interaction. Movements and transitions must occur in a slow, fluid harmony to best achieve the training effects. Breathing and concentration are also included in this adaptation process (WOOD S, 2018).

Precision : Pilates training is concerned with quality, not quantity. Perform the movements correctly instead of repeating a certain one
sometimes increases the quality of movement. Activation and contraction of target muscles at the target time depends on this. In cases where this principle is not enough, training moves away from the integrity within itself (UNGARO A, 2011).

Breathing : It is important to breathe properly during exercise. Breathing is believed to be a catalyst for core stability. Compared with other exercise methods, diaphragmatic breathing is used less in Pilates (LEMOS AQ *et al.,* 2019)
training . The reason for this is the view that increased intra-abdominal pressure during diaphragmatic breathing reduces transversus abdominis muscle activation (MUSCOLINO JE *et al.,* 2004).

Integrated Isolation : To learn correct posture and maximize the benefit to be gained from movement, daily activities must be continued within the framework of centering and other principles (LATEY P, 2001)

Stabilization : Pilates training provides muscular resistance to the *core muscles* and other small stabilizing muscles. Muscular endurance is more important in spinal training than pure muscle strength because the deep spinal stabilizers are constantly at work. At the same time, it facilitates the formation of continuously functioning

memory muscles, which has become routine (LATEY P, 2001; MUSCOLINO JE *et al.,* 2004; LEMOS AQ *et al.,* 2019)

Pilates exercises were designed by *Joseph Pilates* in Germany in 1883. Pilates exercises can have the effect of increasing coordination, improving muscle fiber recruitment, stimulating proprioception and causing muscle co-contraction around large joints. This concept focuses on activating the specific muscle(s) at the correct speed, with quality, precision and conscious control of the movement. Pilates focuses on balance and strengthening of ligaments, joints, seniors have the opportunity to increase their level of functional strength and improve efficiency in daily life (LATEY P, 2001).

The technique, known today as " Pilates " is, basically, an approach of integrated and controlled exercises, with a main focus on body awareness, in which the body and mind mutually influence each other, and this characteristic is what sets the difference with others. other techniques or forms of physical exercise (ROSSI, 2014).

Joseph H. Pilates , its creator, sought, through a system of movements called " *Contrology* ", to exercise as many muscles as possible in a conscious and controlled way. The Method integrates the Western approach - with its emphasis on movement, muscle tone and strength - and Eastern traditions by considering exercise a path to calm emphasizing stretching and flexibility (BARBOSA; *et al.,* 2015 and ROSSI, 2014).

Exercises based on the Pilates method have been used for prevention, rehabilitation, physical conditioning and improvement of mindfulness, associated with well-being (GIACOMINI, *et al.,* 2015 and JUNGES, 2014).

The MP is a comprehensive conditioning method that is based on six fundamental principles that must be performed simultaneously: centralization, concentration, control, precision, breathing and fluidity of movement (MUSCOLINO JE *et al.,* 2004).

Pilates exercises are divided into two broad categories: Mat Pilates and Pilates Apparatus. The first exercises developed on a mat on the floor, later, Pilates created a series of specific devices that make it possible to perform the exercises against resistance, which is provided by the use of springs and pulleys (MUSCOLINO JE *et al.,* 2004).

1.2.1 Rationale for the use of Pilates in the management of dysfunctions caused by Covid-19

One of the fundamental principles of MP is breathing, and its control is fundamental during the execution of the exercises. An essential part of each exercise is learning to breathe correctly, through a full inhalation followed by a forced exhalation. Thus, adequate breathing helps to control movements and, therefore, the method can be considered an indirect strategy for respiratory muscle training. It is known that the incorrect breathing pattern can result in the compensation of lung volumes and respiratory muscle performance, with several factors involved (GIACOMINI, 2016 and IULIAN-DORU T *et al.,* 2013).

Recent studies have shown that PM leads to hypertrophy of the abdominal wall musculature, as assessed by MRI and ultrasound. In view of these findings, the hypothesis that even without the use of a specific training load for the respiratory muscles, the PM may favor an increase in respiratory muscle strength and its performance seems plausible (GIACOMINI, 2016).

Pilates Method has positive results in tone and flexibility, in addition to improving respiratory efficiency. An observational study states that the practice of the Pilates Method improves ventilatory parameters, and may be associated with the stimulation of the ventilatory pattern that the method advocates. In addition, the improvement in VO2 max values is also described, suggesting that the Pilates program produces cardiovascular adjustments that can increase the vascular response to exercise, helping to regulate blood circulation in the musculoskeletal tissue (TINOCO-FERNÁNDEZ *et al.,* 2016) .

1.3 Justifications

Thousands of COVID-19 survivors have experienced the persistence of symptoms including fatigue, pain, dyspnea and musculoskeletal disorders that are known to reduce the functional capacity and, in turn, the quality of life of patients after SARS-COV viral infection - 2 (AZUMA *et al.,* 2020; GREVE, BRECH, *et al.* , 2020 MANDAL *et al.,* 2020). However, although the persistence of symptoms is the subject of recent publications on the post-COVID syndrome, the direct causal relationship

between which factors are associated with the chronification of these symptoms is still not so clear .

Regarding the field of rehabilitation strategies for the management of these disorders, there still seems to be an even greater twilight zone regarding the clear identification of which therapeutic interventions offer real and sustained clinical benefits and are directly associated with the clinical evolution of the syndrome symptoms. post - COVID, or even if certain isolated interventions, using the Pilates method as a unique therapeutic intervention strategy would be effective as a therapeutic intervention for adults with post - COVID syndrome (or who knows post intensive care syndrome, already so well described in the literature and that present a strong intersection with the recently described post-COVID syndrome.

Musculoskeletal disorders and symptoms of dyspnea and fatigue are the most prevalent among survivors of severe forms of COVID-19 and are described as those most common signs and symptoms of post-COVID-19 syndrome. In this syndrome, even after a long period of time elapsed from the acute phase, the presence of symptoms such as respiratory and peripheral muscle weakness , pain, fatigue, dyspnea, exercise intolerance, among others, is observed, in view of the negative repercussions of the systemic manifestations of the disease. COVID-19 with Regarding the quality of life, prognosis and survival of patients, we can say that they have a high use of the Unified Health System (SUS) as the disease progresses.

Pilates exercises , in essence, have clinical and physiological plausibility to be used as a therapeutic tool for the pulmonary and musculoskeletal rehabilitation of these patients.

As it is a new infectious disease with a high risk of severe evolution and hospitalization in an intensive care unit, it is particularly important to explore the clinical characteristics of COVID-19, which can help in the adequate management of its sequelae in the post-acute phase.

Pilates Method exercise program as a rehabilitation tool for these patients affected by the systemic sequelae caused by the infection by COVID-19.

With this, according to Agenda 2030, object 3 - Health and Well-being, we can reduce diseases and comorbidities associated with non-communicable diseases through effective treatment strategies, promoting mental health and well-being.

1.3.1 Relevance to Rehabilitation Sciences

Undoubtedly, the manifestations described in the scope of the post - COVID syndrome brought even more importance to the area of rehabilitation sciences, since thousands of people around the world, in a relatively determined interval, were contaminated by this viral infection, many even developed the severe form and have experienced and are experiencing persistent symptoms of the so-called post-COVID-19 syndrome. Given this scenario, the search for effective, cost-effective and clinically relevant treatment strategies are emerging and fundamental themes for the area of rehabilitation sciences. that we are experiencing and the large number of people affected by COVID-19, the search for more functional rehabilitation resources is of paramount importance for improving the quality of life and adds another resource to our professional activity.

1.3.2 Relevance to the Ministry of Health's Priority Agenda

Given the number of people affected by COVID-19 and thus by the post-COVID-19 syndrome, clinical research involving functional rehabilitation rehabilitation strategies are of paramount importance for improving the population's quality of life and meets axis 4 of the agenda of priorities. of the MS on technological development and innovations in health, as well as meeting axis 9, since the clinical effects of the Pilates method , for example, could be incorporated into the roll of standardized assistance practices of the SUS and thus expand and democratize access to effective interventions and which, in turn, allow expanding the number of users served, since Pilates can and should be done in a group.

1.3.3 Relevance to sustainable development

The most accepted definition of sustainable development is development capable of meeting the needs of the present generation without compromising the ability to meet the needs of future generations. It is development that does not exhaust resources for the future. Social concern is one of the axes of sustainable development and, therefore, clinical research that demonstrates, with solid results, that therapeutic strategies capable of ensuring the expansion of access to the population, have strong relevance for sustainable development.

1.4 Goals

1.4.1 Primary / General

To evaluate the clinical and functional effects of a quarterly Pilates Method exercise program for patients with post-COVID syndrome.

1.4.2 Secondary/Specific

- Evaluate the effects of pilates exercises on muscle strength and peripheral resistance;

- To compare the effects of Pilates on the levels of fatigue and dyspnea in patients with post-COVID syndrome;

- Correlate the effects of Pilates on peripheral muscle function and symptoms of fatigue and dyspnea in patients with post-COVID syndrome.

- Evaluate the effects of Pilates on the quality of life of patients with post-COVID syndrome

1.5 hypotheses

1.5.1 NULL HYPOTHESIS (H0)

Pilates Method exercise program has no clinical effect on peripheral muscle strength and endurance and does not reduce fatigue or dyspnea in patients with post-COVID syndrome.

1.5.2 ALTERNATIVE HYPOTHESIS (H1)

A quarterly Pilates Method exercise program has clinical effects on peripheral muscle strength and endurance, reducing fatigue and dyspnea in patients with post-COVID syndrome.

CHAPTER 2 - Participants and Methods

2.1 Ethical aspects

This clinical trial will be submitted to the Ethics and Research Committee of UNISUAM before the execution of the study, in accordance with resolution 466/2012. All voluntary participants, after all clarifications, will sign an informed consent form (ICF; Appendix 1) after being informed about the nature of the study and the protocol to be carried out.

2.2 Study design

The study will be a clinical trial previously randomized by electronic randomization system (www.random.org) and the allocation of volunteers in the study arms will be done without the participation of the researchers. The study will be double-blind since neither the volunteers nor the professional who will perform the pilates protocol are aware of the objectives and clinical valences that will be measured by the study.

2.2.1 Location of the study

The clinical trial will be carried out at the Rehabilitation Center of the Military Police of the State of Rio de Janeiro

2.2.2 Protocol pre -registration

After approval by the UNISUAM Research Ethics Committee, the entire clinical trial protocol will be registered in the Brazilian Registry of Clinical Trials (ReBEC - https://ensaiosclinicos.gov.br/) or in the *Clinical trials* (https://clinicaltrials.gov/)

2.3 Sample

The sample will consist of 60 participants, divided into two groups: an intervention group (n=30) that will do a 12-week program, 2x/week of Pilates method exercises , and a control group (n=30) that will not do any intervention for rehabilitation in the period.

2.3.1 Study recruitment site

Patients will be recruited at the Central Hospital of the Military Police and at the specialized multidisciplinary outpatient post-COVID-19 follow-up.

2.3.2 Inclusion criteria

1. Patients with a previous diagnosis of COVID-19, who required hospitalization and required invasive mechanical ventilation for at least 7 days and who were discharged between August and December 2021 to minimize regression to mean;
2. Both sexes;
3. Older than 18 years.

2.3.3 Exclusion criteria

1. Need for supplemental home oxygen;
2. Motor or neurological or cognitive alteration that contraindicates the practice of Pilates .
3. Persistence of clinical signs of deep vein thrombosis
4. Upper limb dynamometry < 14 kg for men and < 7 kg for women would indicate very marked peripheral muscle weakness and would therefore contraindicate Pliates at the moment.

2.3.4 Risks and Benefits

The possible risks of this research are, the increase in the sensation of shortness of breath during the execution of the exercises, the reduction of the saturation of O2 and, the possible muscular pains resulting from the practice of the Pilates Method .

As benefits we can mention: the improvement of the disposition to carry out the activities of daily living, the improvement of the balance, in addition to obtaining gains in relation to the quality of life and the reduction of dyspnea.

The research will be immediately suspended if any risk or damage to the health of the subject participating in the research is perceived, resulting from it, not provided for in the consent form (ICF). If it is proven that a group has benefited from the intervention of the protocol of this work, the same intervention will be offered to the other group, avoiding any harm to the patient.

Proposed Procedures/Methodology

2.3.5 clinical evaluation

- Demographic and clinical characteristics: An initial assessment will be carried out, where personal data and clinical history will be collected.

2.3.6 Peripheral Muscle Assessment

2.3.6.1 Palm grip dynamometry

Traditionally, handgrip strength (HGS) tests have been used in rehabilitation to assess the physical condition of the upper limbs, by measuring the strength of the hand and forearm muscles of patients with various disorders in the upper extremity resulting from arthritis. rheumatoid disease , carpal tunnel syndrome, lateral epicondylitis , stroke, traumatic injuries, myopathy , ICU-acquired muscle weakness, critical patient polyneuropathy and neuromuscular diseases (INNES E, 1999; KURILLO GA *et al* ., 2004; MOREIRA D *et al., 2004; MOREIRA D et al. al* ., 2003) HGS measurement by

dynamometry presents a good correlation with the functional level of the upper limbs and general health status, being widely used in the selection of therapeutic procedures and monitoring of functional rehabilitation (INNES E, 1999). Manual dynamometry has wide applicability, as it is a low-cost, simple, fast and non-invasive method (GÜNTHER CM *et al* ., 2008) that provides, through HGS values, an indicator of the general health of the evaluated individuals.

The HGS assessment will be performed by a single previously trained investigator, in the morning between 8 am and 12 noon, according to the recommendations of the Brazilian Society of Hand Therapists (SBTM, 2008). The individuals will be positioned seated with the arm adducted parallel to the trunk, shoulder in neutral rotation, elbow flexed at 90°, forearm in fundamental position. Wrist hyperextension of up to 30º and ulnar deviation of up to 15º will be allowed during the tests. Three measurements will be taken from both hands, with a minimum interval of 30 seconds between them. The tests will be performed alternately between the dominant and non-dominant side, to minimize the influence of muscle fatigue. For data analysis, the highest value obtained for each hand will be considered. The dominant hand is defined as the preferred hand for carrying out daily activities. Volunteers will be asked which hand they prefer to carry out activities such as writing, eating and carrying objects. During the execution of the handgrip, the arm will remain immobile, with only permission for the movement of the wrist and finger joints.

Will be used as prediction formulas (NOVAES RD *et al.,* 2009):

- HGS-D, $_{kgf}$ = 39.996 - (0.382 x age, $_{years\ )}$ +(0.174 x weight, $_{kg}$)+(13.628 x sex (men=1; women=0)
- HGS-ND, $_{kgf}$ = 44.968 - (0.420 x age, $_{years}$)+(0.110 x weight, $_{kg}$)+(9.274 x sex (men=1; women=0)

2.3.6.2 Quadriceps Maximum Load Test

The one-repetition maximum test (1RM) is often used as a measure of muscle strength, whether in the context of physical rehabilitation. In this sense, there is a consensus that the basis for prescribing therapeutic exercises, especially those

performed against resistance TCR) is established through the relationship between the percentage of 1RM and the number of repetitions.

The 1 RM Test will be performed in an extension chair, with adjustments that keep the hip and ankle flexed at 90º and the knee flexed to ensure an angular trajectory of 120º after extension. The 1RM tests will be conducted according to the protocol proposed by Brown and Weir (Brown & Weir, 2001). Before each test, free, light activities involving the tested muscle will be performed, followed by 1 min of stretching for the tested muscle (in this case, the quadriceps will be tested). After stretching, 3 repetitions were performed with moderate load and after 5min of rest and interval, the 1RM test will be performed, adding weights when necessary, 0.4 to 5kg, totaling up to five attempts. We will record the maximum load as the greatest load lifted in a single movement of full knee extension in an open kinetic chain.

For the reference values, the highest value among the three measures of maximum voluntary contraction in the 1RM test, normalized by the body weight of each individual tested, was used, according to the formula proposed by Magalhães in 2010: (Strength (Kg) /Weight x 100)

2.3.6.3 Quadriceps Muscle Endurance Test

The quadriceps muscular endurance test will be performed after 30 min of rest after the 1 RM test. We will use a load of 40% of the load obtained in the 1 RM test, rounding up to the next higher load in case of load fractions.

The muscular endurance test will be performed in the same extension chair, with hips, ankle at 90º and knee flexed to ensure an angular velocity of 1'20º/s using the dominant lower limb (LLd). Volunteers will be instructed to count 1 second for LL extension and 1 second to return to flexion (angular velocity of 120º/s). The outcome of this test will be the time to exhaustion characterized by failure or inability to complete the range of motion.

2.3.7 Post COVID functional scale (PCFS)

The Post-COVID-19 Functional Status Scale is a longitudinal patient assessment tool for identifying changes in post-COVID-19 functional status and their evolution. The PCFS scale covers the entire set of functional areas, in particular limitations in activities of daily living (ADL) and in the workplace, as well as changes in lifestyle. The scale can be administered to the patient by trained staff or conducted by the patient as a self-assessment. In the project, following the guidelines of the PCFS, which will be used for research purposes, it will be conducted by a trained evaluator and followed all the guidelines described for this purpose. This scale consists of six ordinal categories that reflect conditions of increasing severity, from 0 to 4. Death is coded as "D". Grade 0 implies the absence of any residual symptoms. If one or more residual symptoms are present but do not affect the patient's normal activities, grade 1 will be assigned. If they are limited in intensity/frequency or occasionally avoided, grade 2 will be assigned; grade 3 implies limitations that force the patient to reprogram usual activities, reflecting the inability to perform some of them, which, in fact, must be performed by others. Grade 4, the most severe, is reserved for severe functional restrictions that require continuous assistance in daily activities (CORSI *et al.,* 2020; KLOK *et al.,* 2020) .

2.3.8 Dyspnea assessment by the modified Medical Resource scale Council (mMRC)

medical resource modified dyspnea scale *council* (mMRC): consists of only five items, and the patient chooses the item that corresponds to how much dyspnea limits their ADLs . The patient reports his subjective degree of dyspnea by choosing a value between 0 and 4, where 0 (suffers from shortness of breath only during intense exercise), 1 (suffers from shortness of breath when walking quickly, climbing stairs or ramps), 2 (walks slower than people of the same age because of shortness of breath or having to stop for breath even when walking slowly), 3 (to breathe after walking less than 100 m or after a few minutes) and 4 (feel so short of breath who doesn't leave the house anymore, or I need help dressing or bathing alone) (ANNEX 1). The mMRC dyspnea scale showed satisfactory reliability and validity (KOVELIS *et al.,* 2008) .

For the perception of effort during the exercises of the intervention group, the modified Borg scale will be used : which is a subjective scale to qualify the degree of

respiratory distress during exercise, where option 0 means no effort and 10 means maximum effort and will be used exclusively during Pilates sessions to control exercise intensity.

2.3.9 Fatigue Assessment by the Fatigue Pictogram

Fatigue assessment will be done by the Fatigue Pictogram. The Fatigue Pictogram (FITCH MI *et al.,* 2003) is an illustrated instrument for the assessment of fatigue (ANNEX 2). It has two sets of figures that assess the intensity and impact of fatigue on usual activities and, as it is brief and easy to apply, it is useful for assistance and research. Aiming at comparability between world populations or populations with different diseases, and in view of the recommendations to make cultural adaptations of existing instruments instead of creating new ones, we chose to use it, assigning numbers to each of the images to facilitate quantitative analysis. This scale was validated in Brazil in relation to its psychometric properties in the Brazilian population (MOTA DD *et al.,* 2009)

2.3.10 Quality of life assessment

The assessment of quality of life will be carried out using a generic instrument of 36 items, validated in Brazil and called the SF-36 (Short Form Health Survey). This instrument is a generic quality-of-life assessment questionnaire that is easy to administer and understand. Consisting of 36 items, subdivided into 8 domains, which are: functional capacity, physical aspects, pain, general health status, vitality, social aspects, emotional aspects and mental health. It presents a score that goes from 0 (zero) to 100 (obtained by calculating the *Raw Scale),* where zero corresponds to the worst general health status and 100 corresponds to the best health status. To calculate the domain (aspect to be analyzed), a specific formula is applied, according to the translated and validated SF-36 (Brazier *et al.* , 1992; Lins and Carvalho, 2016)

2.3.11 Pilates Method Exercise Protocol (MP)

Pilates exercise protocol : was developed based on protocols contained in previously published clinical trials whose objective was muscle strengthening or improvement of muscle fatigue. Thus, the protocol developed will perform exercises from the classical repertoire of the Pilates Method , with the use of equipment exclusive

to the Method - such as *Cadillac , Lader Barrel , Chair and Reformer* . The sessions will take place twice a week, in groups of up to 3 participants, always in the morning and will last 60 min, with 10 min of warm-up, 40 min of exercises with load and 10 min of relaxation exercises and calm down. All sessions will be performed by a physical therapist specialized in the method, in a specific outpatient clinic. The professional who will conduct the Pilates sessions will execute the proposed protocol and is unaware of the outcomes studied by the project. In figure 3, we present the equipment that will be used in the study.

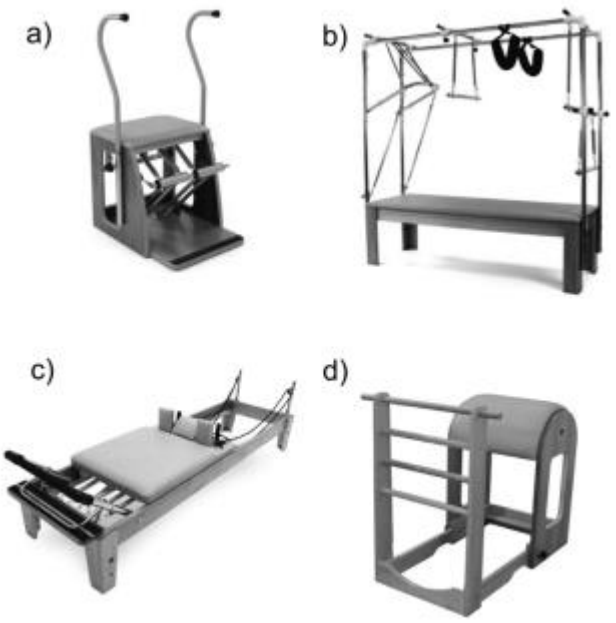

Figure 3: Equipment that will be used. (a) *Combo Chair* , (b) *Cadillac ,* (c) *Universal Reformer* , (d) *Ladder barrel*

2.4 Outcomes

2.4.1 primary outcome

As variables for the primary outcome of this research, it will be the functional performance, resulting from the combination of the PCFS Scale with the Dynamometry of Pressure Para, Test of Strength and of Endurance of the quadriceps muscle.

2.4.2 secondary outcome

Improved quality of life (Questionnaire SF36) and reduced perception of dyspnea during physical activities and ADLs (mMRC and Borg).

2.5 Data analysis

2.5.1 Sample size (calculation or justification)

The sample size calculation was done with the " pwr " package (CHAMPELY S, 2018) (R package , version 1.2-2, https://CRAN.R-project.org/package=pwr). For the calculation, we considered the mean of 41.3, the standard deviation of 5.05 and a minimal clinically important difference of 4.7 kg between the means of maximum load in the maximal voluntary contraction test (OLIVEIRA IO, 2016) and power based on *Cohen 's model* of 0.8 with a standard deviation of 5.05. Assuming α = 0.05, β = 0.8, standard deviation = 5.05 and an effect size proposed by Cohen of 0.93.

This effect size " *d* " is calculated by:

d= [(Reference average + Minimum detected change) – reference average]/ deviation – standard

d= [(41.3 + 4.7) – 41.3]/5.05 => d= 0.93.

pwr package . in R we have:

n= pwr.t. test (n=NULL, d=0.93, sig.level =0.05, power=0.8, type=" two.sample ", alternative=" two.sided ")

n = 19.15925

d = 0.93

sig.level = 0.05

power = 0.8

alternative = two.sided

In this way, we use on=established and rounded up to the first integer immediately higher (n=20) + 20% to cover any losses. Thus, the minimum number of patients needed in each group will be 24 patients.

2.5.2 control variables

The control variables will be the peripheral muscle strength established by the handgrip test, by the maximum voluntary contraction test and by the peripheral muscle endurance test. In addition, we will use the mMRC , the quantified fatigue pictogram, the PCFS and the quality of life as control variables.

2.5.3 Exposure variables

The exposure variables will be the 12-week, twice-weekly exercise program based on the Pilates method .

2.5.4 Confounding variables

The length of stay and the degree of dysfunction acquired in the ICU may represent confounding variables. Thus, avoiding regression to the mean, inclusion in the study can only occur after 3 months (90 days) after hospital discharge. This is the time described to minimize eventual complications inherent to the immobility syndrome and homogenize the groups

2.5.5 Statistical analysis plan

Data analysis will be performed using the SPSS 23.0 program (Statistical Package for Social Sciences). Descriptive analysis will be performed for all variables (mean and standard deviation). General Linear Model (GLMs) with mixed design will be performed to compare treatment effect size between groups. The pairwise comparison comparisons) will be performed to verify the mean difference between the Pilates Group and the Control Group in all variables in each period independently.

Intention-to-treat analysis was used using the *Last method. observation Carried Forward* (LOCF) for lost participant data. A significance level of 0.05 and a confidence interval of 95% will be adopted

.

2.5.6 Availability and access to data

All data may be made available for consultation and *full access* at the clinical trial registration site.

2.6 Expected results

The hypotheses of this clinical trial hope to demonstrate the clinical effects of a Pilates program for the management of musculoskeletal disorders and persistent symptoms in patients with COVID-19. Studies involving other populations have already demonstrated the effects of Pilates on peripheral muscle strength and *endurance* in patients with chronic lung disorders, patients with chronic low back pain, patients with neurological syndromes, among others. Thus, it is hypothesized that similar effects may occur in the study population.

2.7 Budget and financial support

This study will be entirely with own resources and equipment available in the research laboratories of the teaching institution partner in conducting the study. There is no burden to study participants

Table 3: Budget details.

Budget identification	Type	Price R$)
Physiotherapist specializing in Pilates	execution team	BRL 0.00
reformer	permanent material	BRL 0.00
Cadillac	permanent material	BRL 0.00

Chair	permanent material	BRL 0.00
Lader barrel	permanent material	BRL 0.00
pulse oximeter	permanent material	BRL 0.00
stopwatch	permanent material	BRL 0.00
palm grip dynamometer	permanent material	BRL 0.00
Extension chair and load cell	permanent material	BRL 0.00
Video camera	permanent material	BRL 0.00
Reproduction of evaluation sheets	Material consumption	BRL 50.00
A4 paper format	Material consumption	BRL 50.00
	Total in BRL	BRL 100.00

2.8 Timeline

Table 4: Execution schedule.

step identification	Start (mm/yy)	Term (mm/yy)
Beginning of the course and designing the project	August/20	November/21
Project submission to the Research Ethics Committee	April/22	April/22
Methods training	April/22	April/22
patient recruitment	April/22	May/22
Execution of the Protocol	April/22	July/22
Data collection and tabulation	April/22	July/22
Data analysis	July/22	August/22
Preparation of the manuscript(s)	August/22	August/22
Final essay writing	August/22	August/22
defense exam	September/22	September/22
Changes guided by the examining board	September/22	September/22
Submission of manuscript(s)	September/22	October/22
Delivery of the final version of the final paper	October/22	October/22

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Appendix 1 - Free and Informed Consent Form

EFFECTS OF PILATES ON PERIPHERAL MUSCLE STRENGTH, DYSPNEA AND FATIGUE IN PATIENTS WITH POST-COVID-19 SYNDROME: CONTROLLED AND RANZOMIZED CLINICAL TRIAL

Made from Res. nº 466 of 12/10/2012 of the National Health Council

Brief justification and research objectives : We are daily in contact with the negative repercussions of the sequelae caused by the COVID-19 infection. Complaints such as shortness of breath, tiredness, body aches, joint pain and weakness, worsen the quality of life and make daily activities difficult. Pilates exercises can be used to reduce these discomforts, improving quality of life and maintaining independence. The objective of this research is to evaluate the clinical and functional effects of the Pilates Method exercise program for post-COVID patients.

Procedures : In a first contact, a draw will be held to define which group you will be placed in. We will have two groups, in Group 1, the Pilates Method protocol will be applied , 2x/week in a period of 12 weeks with 60-minute sessions; Group 2 will only undergo initial and final assessments. After defining the group you will be a part of, we will make an initial assessment, where your personal data, disease history, medication use, life habits and information about the Covid-19 infection will be collected. After this assessment, you will answer 2 questionnaires, one specific about the consequences of Covid-19 and another about quality of life. In a third step, we will measure your blood pressure and check your oxygen saturation and heart rate, after these measurements we will do some physical tests to assess your tiredness and balance in carrying out some movements similar to your daily life, such as sitting and getting up. . We will always be monitoring your feeling of shortness of breath and tiredness, in addition to the vital signs measured in the second stage. After this evaluation, Pilates Apparatus sessions will be scheduled twice a week, for 3 months, where a Pilates exercise protocol will be applied in the specific equipment of the Method - Cadillac , Chair , Lader Barrel and Reformer .

Potential risks and benefits : The possible risks are, increased sensation of shortness of breath during the execution of the exercises, drop in O2 saturation, possible muscle pain resulting from the practice of Pilates . As benefits we can mention: improved disposition to perform day-to-day functions, improved balance, in addition to obtaining gains in terms of quality of life and reducing the feeling of shortness of breath. If it is proven that a group has benefited from the intervention of the protocol of this work, the same intervention will be offered to the other group, avoiding any harm to the patient.

Guarantee of secrecy, privacy, anonymity and access: Your privacy will be respected, that is, your name or any other data or element that can in any way identify you, will be kept confidential. Anonymity and privacy will be guaranteed. If there is interest, you will have access to the results.

Ensuring clarification : Assistance is ensured throughout the research, as well as the guarantee of your free access to all information and additional clarifications about the study and its consequences.

Assurance of responsibility and disclosure : The results of the exams and research data will be the responsibility of the researcher, and these results will be published in the scientific environment without citing any way that can identify their name.

Expense reimbursement guarantee : You will not incur personal expenses at any stage of the study, nor financial compensation related to your participation. In case of personal injury directly caused by the procedures proposed in this study, you will be entitled to medical treatment, as well as the legally established indemnities. However, if you have any expenses resulting from participation in the research, there will be reimbursement by means of a deposit in a checking account or check or cash. Likewise, if any damage occurs as a result of your participation in the study, you will be duly compensated, as determined by law.

Responsibility of the researcher and the institution : The researcher and the proposing institution will be responsible for any personal or moral damages related to the physical and ethical integrity that the research may entail.

Criteria for suspending or terminating the research : The study will be suspended in the event of any methodological or technical failure observed by the researcher, and the researcher is responsible for informing all participants of the reason for suspension. The study will also be suspended if any risk or damage to the health of the participating subjects is perceived, resulting from the research, which has not been foreseen in this term. When the necessary data collection is reached, the survey will be terminated.

Infrastructure statement : The institution where the study will be carried out has the necessary infrastructure for the development of research with an adequate environment.

Ownership of the information generated: There is no restrictive clause for the dissemination of research results, and the data collected will be used solely and exclusively to prove the experiment. The results will be submitted for publication, whether they are favorable or not to the hypotheses of the study.

About the refusal to participate : If you wish, you may refuse to participate in the study, or withdraw your consent at any time, without having to justify yourself, not suffering any damage to the assistance you receive.

Contact of the responsible researcher and the ethics committee : At any stage of the study, you can have access to the responsible professional, MICHELLE DE AGUIAR ZACARIA , who can be reached at (41) 98427-6132 . If you have any concerns or questions about research ethics, you can contact the Research Ethics Committee of Centro Universitário Augusto Motta (UNISUAM), located at Rua Dona Isabel, 94 – Bonsucesso, telephone (21)3882-9797 (Extension: 9943), e-mail: comitedeetica@souunisuam.com.br.

If this term is clear enough to provide you with all the information about the study and if you understand its purposes, the procedures to be carried out, its discomforts and risks, the guarantees of confidentiality and permanent clarification. You may declare your free consent to participate, being fully aware of the study proposals.

Rio de Janeiro, _____ of _____ of _____

_____

Signature of the participant or the person in charge

Appendix 2 - Preliminary Ethical *Checklist (* CEPlist)

The *List of Items for the Research Ethics Committee* (*CEPlist*) was prepared based on Resolution of the National Health Council No. 466 of December 12, 2012 with the aim of improving the quality of information in Research Protocols involving human beings that are submitted for consideration by the CEP/CONEP system.

The *CEPlist* is completed by the main researcher of the project before its submission to be attached to Plataforma Brasil as "Other" documents. The researcher will fill in the number of the page where this information appears. If the item does not apply, it must be filled in with "NA".

a) Mandatory documents		**Pages**
a.1. Terms	a) Term of Consent of the proposing institution written on letterhead, dated and signed by a representative	
	b) Term(s) of Consent of the co-participating institution(s) written on letterhead, dated and signed by a representative	
	a) Free and Informed Consent Form	
	b) Free and Informed Consent Term	
	c) Term of Authorization for Use of Secondary Data	
a.2. Timeline	a) Detailed schedule regarding the stages of the research project	
a.3. Budget	a) Detailed budget regarding the application of resources	
	b) Citation of the research sponsor(s)	
a.4. declarations	a) Declaration of Institution and Infrastructure written on letterhead, dated and signed by a representative	
	b) Declaration of Researchers	
	c) Sponsor's Declaration	
a.5. waiver	a) Justification for waiver of the Term requested by the responsible researcher to the CEP/CONEP System	
b) Research Project (PP)		**Pages**
b.1. Introduction	a) Grounding on scientific facts, prior experimentation and/or assumptions appropriate to the specific area of research	
b.2. Materials and methods	a) Appropriate methods to answer the questions studied, specifying them, whether qualitative, quantitative or quali -quantitative research	
	b) Calculation and/or justification of sample size	
	c) Well-defined inclusion and exclusion criteria	
	d) Detailed procedure for recruiting participants	
	e) Location(s) of the research stage(s)	
	f) *Wash - out* periods or use of placebo justified and with critical risk analysis	

	g) Detailed and justified explanation of the exams and tests that will be carried out	
	h) Maintenance of research data in a file, physical or digital, under the custody and responsibility of the main researcher, for 5 years after the end of the research	
	i) Detailed criteria for suspending and terminating the survey	
b.3. Appendices and Annexes	a) Questionnaire(s) for data collection	
c) Free and Informed Consent Term (ICF)		**Pages**
c.1. Required information	a) Project title below the Term title	
	b) Information provided in clear and accessible language to the participant	
	c) Justification and clear and well-defined objectives	
	d) Detailed procedures and methods to be used in the research	
	e) Possibility of inclusion (draw) in a control or experimental group	
	f) Possible discomforts and risks arising from participation in the research	
	g) Possible benefits arising from participation in the research	
	h) Measures and precautions to be taken to avoid and/or reduce adverse effects and conditions that may cause damage	
	i) Forms of follow-up and assistance to which research participants will be entitled to deal with complications and damages resulting, directly or indirectly, from the research	
	j) Guarantee of full freedom to the research participant, to refuse to participate or withdraw their consent, at any stage of the research, without penalty	
	k) Ensuring that the confidentiality and privacy of research participants is maintained during all phases of the research	
	l) Guarantee that the research participant will receive a copy of the Term	
	m) Guarantee of reimbursement and how the expenses incurred by the research participants and resulting from it will be covered	
	n) It explains the guarantee of indemnity in the face of possible damages resulting from the research	
	o) Clarification on the possibility of including the participant in a control or placebo group,	

	clearly explaining the meaning of this possibility	
	p) Commitment to forward the research results for publication in the scientific environment	
	q) Statement by the responsible researcher that expresses compliance with the requirements of Resolution No. 466/2012	
	r) Declaration by the responsible researcher that the results of the exams and/or research data will be the responsibility of the researchers	
c.2. Researcher	a) All pages and copies of the Term include the address and telephone or other contact information of those responsible for the research	
c.3. Ethics Committee	a) On all pages and copies of the Term, the address and telephone or other contact information of the CEP	
c.4. Participant	a) There is space for the name of the participant and/or legal guardian and place for their signature	
d) Free and Informed Assent Term (TALE)		**Pages**
d.1. Presentation	a) There is a consent form for those responsible with the consent of minors or legally incapable persons.	
recommendations		
( ) Approved *This project complies with Resolution 466/2012 of the National Health Council and can be submitted to the CEP/CONEP*	**( ) With pending** *A review of the suggestions proposed by the board is requested before consideration by the CEP/CONEP*	**( ) Failed** *The project must be resubmitted after meeting the suggestions proposed by the BANK and the CEP/CONEP criteria*

Appendix 3 - Image use authorization term

I, _____, nationality _____, minor, in this act duly represented by his (her) (legal guardian), _____, nationality _____, marital status _____, bearer of Identity Card RG No. , resident at Av /Rua _____, no. _____, municipality of Rio de Janeiro _____/Rio de Janeiro, I AUTHORIZE the use of my image in any and all material including photos, videos and documents, to be used in didactic and scientific material arising from the EFFECTS OF PILATES ON PERIPHERAL MUSCULAR STRENGTH, IN DYSPNEA AND FATIGUE OF PATIENTS WITH POST-COVID-19 SYNDROME: CONTROLLED AND RANZOMIZED CLINICAL TRIALS. This authorization is granted free of charge, covering the use of the aforementioned image throughout the national territory and abroad, in the following ways: presentation folder; scientific articles in specialized magazines and newspapers; classes in training courses; informational posters; lectures at scientific meetings; congress banners; electronic media (panels, videos, television, cinema, radio program, among others), as long as they are related to the dissemination of the project and the research findings. As this is the expression of my will, I declare that I authorize the use described above without anything to be claimed as rights related to my image or any other, and I sign this authorization in 2 copies of equal content and form. **I declare that I understand the objectives and benefits of using the research images and I authorize their use in the ways described above, for the dissemination of the project and the research findings**.

_____ Date: _____/_____/_____
Participant's signature

_____ _ Date : _____/_____/_____
MICHELLE DE AGUIAR ZACARIA

Appendix 4 – Research Consent Term

The MILITARY POLICE PHYSIATRY AND REHABILITATION CENTER is in agreement with the execution of the project on the **EFFECTS OF PILATES ON PERIPHERAL MUSCLE STRENGTH, DYSPNEA AND FATIGUE IN PATIENTS WITH POST-COVID-19 SYNDROME: CONTROLLED RANDIMIZED CLINICAL TRIAL**, coordinated by researcher **PROFESSOR DR. LUIS FELIPE DA FONSECA REIS** AND BY MASTER STUDENT MICHELLE DE AGUIAR ZACARIA, from the Postgraduate Program in Rehabilitation Sciences at Centro Universitário Augusto Motta, and undertakes to support the development of said research in this Institution, ALLOWING THE PROJECT EXECUTION, WITHOUT ANY FINANCIAL OR EVEN ADMINISTRATIVE CHARGES IN THE ROUTINE OF THE UNIT. This institution is committed to ensuring the safety and well-being of participants in compliance with Resolution 466 of 2012 of the National Health Council and its complementary ones.

Rio de Janeiro, March 30, 2022.

TEN CEL PM MED SIRLEY DE MELLO FERNANDES

RG 60686 ID FUNCTIONAL 2462256-7

DIRECTOR OF THE PHYSIATRY AND REHABILITATION CENTER OF PMERJ

( ) I authorize the realization of the Project on the premises of the CFRPM

( ) I authorize to cite the name of the Institution

Annex 1 - Post-COVID-19 Functional Status Scale (PCFS)

How much are you currently affected in your everyday life by COVID-19? (Please indicate which one of the following statements applies to you most)	Corresponding PCFS scale grade
I have no limitations in my everyday life and no symptoms, pain, depression or anxiety related to the infection.	0
I have negligible limitations in my everyday life as I can perform all usual duties/ activities, although I still have persistent symptoms, pain, depression or anxiety.	1
I suffer from limitations in my everyday life as I occasionally need to avoid or reduce usual duties/activities or need to spread these over time due to symptoms, pain, depression or anxiety. I am, however, able to perform all activities without any assistance.	2
I suffer from limitations in my everyday life as I am not able to perform all usual duties/ activities due to symptoms, pain, depression or anxiety. I am, however, able to take care of myself without any assistance.	3
I suffer from severe limitations in my everyday life: I am not able to take care of myself and therefore I am dependent on nursing care and/or assistance from another person due to symptoms, pain, depression or anxiety.	4

Annex 2 - Medical Research Dyspnea Scale modified council

Scale	Severity of dyspnoea
0	No breathlessness except with strenuous exercise
1	Shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 metres or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

Annex 3 - Fatigue Pictogram