ARTICLE ORIGINAL

Long COVID outpatient rehabilitation: a call for action

Reabilitação ambulatorial da COVID longa: uma chamada à ação

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ABSTRACT

COVID-19 has motor, cognitive, psychological and nutritional consequences that require rehabilitation. **Objetive:** To describe the outpatient rehabilitation program developed at the Instituto de Medicina Física e Reabilitação do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. **Method:** We collected sociodemographic and clinical data of 12 adults with laboratory-confirmed COVID-19, severe and critical, who needed hospitalization in the acute phase. Functional assessments included Functional Independence Scale (FIM), EQ-5D-5L, World Health Organization Disability Assessment Schedule (WHODAS 2.0), Post-COVID-19 Functional Status scale (PCFS), Medical Research Council (MRC) dyspnea scale, visual analog scale (VAS) for pain, Douleur Neuropathique 4 (DN-4), Epworth sleepiness scale, Insomnia Severity Index, Montreal Ontario Cognitive Assessment (MoCA), Depression, anxiety and stress scale (DASS-21), nutritional assessment, Timed Up and Go test, 10-meter walking test (10 MWT), handgrip strength, MRC sum score, musculoskeletal ultrasound of the thigh.The outpatient rehabilitation program included electrical and musculoskeletal inductive magnetic stimulation, extracorporeal shockwave treatment, isokinetic exercises, emotional approach, cognitive stimulation, occupational performance stimulation, nutritional guidance, and educational program by COMVC mobile application. Individualized program was delivered twice a week until pre-stablished discharge criteria was achieved. **Results:** VAS and TUG presented statistically significant improvements ($p < 0.001$). PCFS, FIM, handgrip strength, 10 MWT and DASS-21 anxiety presented slopes in the direction of improvement. **Conclusion:** The optimized, intensive, interdisciplinary and short-term outpatient rehabilitation program improves pain, mobility and anxiety in long COVID patients.

Keywords: COVID-19, Rehabilitation, Treatment Outcome, Patient Care Team, Rehabilitation Centers

RESUMO

A COVID-19 tem consequências sensório motoras, cognitivas, psíquicas e nutricionais que necessitam de reabilitação. **Objetivo:** Descrever o programa de reabilitação ambulatorial desenvolvido no Instituto de Medicina Física e Reabilitação do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, otimizado, intensivo e de curta duração. **Método:** Obtivemos informações sociodemográficas e clínicas de 12 adultos com diagnóstico laboratorial de COVID-19, grave e crítica, que necessitaram de hospitalização na fase aguda. Avaliações funcionais: Escala de Medida de Independência Funcional (MIF), EQ-5D-5L, World Health Organization Disability Assessment Schedule (WHODAS 2.0), Post-COVID-19 Functional Status scale, Medical Research Council (MRC) dyspnea scale, escala visual analógica (EVA) para dor, DN-4 (Douleur Neuropathique 4), escala de sonolência de Epworth, Índice de Gravidade da Insônia, Montreal Ontario Cognitive Assessment (MoCA), escala de Depressão, ansiedade e estresse (DASS-21), avaliação nutricional, Timed Up and Go, teste de caminhada de 10 metros, teste de preensão palmar, MRC sum score, ultrassonografia musculoesquelética da coxa antes, durante e após programa de reabilitação ambulatorial. Este incluiu estimulação magnética indutiva e elétrica musculoesquelética, tratamento por ondas de choque extracorpóreas, exercícios isocinéticos, abordagem emocional, estimulação cognitiva, estimulação do desempenho ocupacional, orientação nutricional e programa educacional por aplicativo COMVC. O tratamento foi realizado duas vezes por semana até atingir os critérios de alta pré-estabelecidos. **Resultados:** VAS e TUG proporcionaram melhora estatisticamente significante ($p < 0,001$). PCFS, MIF, Handgrip, 10 MWT e DASS-21 domínio ansiedade apresentam tendências de melhora**. Conclusão:** O programa melhora a dor, mobilidade e ansiedade em pacientes com COVID longa.

Palavras-chaves: COVID-19, Reabilitação, Resultado do Tratamento, Equipe de Assistência ao Paciente, Centros de Reabilitação

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INTRODUCTION

COVID-19 is an infectious disease due to viral coronavirus infection 2 (SARS-CoV-2) and there is growing evidence that coronavirus viruses are neuroinvasive and spread to extra respiratory organs, including the central nervous system.[1]

Patients who survive a hospitalization to manage the acute and severe cases of COVID-19 presented high rates of depression, anxiety, posttraumatic stress disorder associated with insomnia, intense fatigue, and muscle weakness.[2,3]

Since some of the effects may manifest months or years after infection, consistent follow-up with patients who have been affected by COVID-19 will be required. Keeping accurate records of these patients with functional impairments may allow establishing plausible connections with aging-associated neurodegenerative diseases such as Parkinson's disease in the future. This possibility was raised because there seems to be an association between SARS-CoV1 and a higher risk of developing Parkinson's disease and multiple sclerosis.[4]

Other neurological symptoms and subclinical cognitive dysfunctions after COVID-19 infection may result from multiple and interactive causes, notified due to direct damage of the virus to the cortex and adjacent subcortical structures, generating systemic impairment and psychological traumas.[5,6]

The nervous system's symptoms and neurological disorders associated with the COVID-19 infection have been identified. Such symptoms and disorders include loss of taste and smell, headache, disorientation, changes in mental status, delirium, encephalopathy, epileptic seizures, musculoskeletal disorders, ischemic or hemorrhagic stroke, thrombosis, and Guillain-Barré syndrome.[7]

It is rather likely that the storm of cytokines and insults to the brain through small or large strokes or even high levels of inflammation within the brain will have severe consequences with great potential for disabling manifestations in the medium and long term.[1,8-16]

Hence, health systems around the world may experience a wave of patients with depression, posttraumatic stress disorder, anxiety, insomnia, or psychosis, as well as cognitive impairment or cognitive decline in the coming years.[4]

Thornton[6] brings the challenge of rehabilitation in treating these patients after severe hospitalization. After intensive care, the rehabilitation of thousands of people is not natural or expected. Also, severe muscle loss, physical deconditioning, sleep disorders, severe fatigue, memory problems, anxiety, depression, and posttraumatic stress are the sequelae of the infection.

Unfortunately, Brazil has become one of the countries with the highest number of cases and mortality worldwide. The World Health Organization data shows updated figures (*https://covid19.who.int/region/amro/country/br*).[17] It is noticeable that the country has many risk groups listed by the World Health Organization, such as the elderly and individuals with comorbidities.[18] Also, given Brazil's continental dimensions, the populations of each region have different characteristics such as social behaviors, genetic and economic characteristics, demanding diverse medical and social controls in each region.[19]

Facing such needs, specifically in the southeast region of the country, the Instituto de Medicina Física e Reabilitação do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (*Institute of Physical Medicine and Rehabilitation of the General Hospital of the Medical College of the University of São Paulo)* – (IMREA HCFMUSP, in its Portuguese acronym) together with the Rede de Reabilitação Lucy Montoro (*Lucy Montoro Rehabilitation Network*), which values multidisciplinary/interdisciplinary rehabilitation care for various types of disabilities,[20] included, more recently, multidisciplinary interventions for patients with COVID-19 sequelae.[21]

Understanding how much the institutional rehabilitation program can influence the recovery of these individuals becomes necessary. It is known that COVID-19 is oppressive to health services and professionals worldwide.[22] Concerning rehabilitation, global care in response to COVID-19 requires environmental changes, generating new interactions for health professionals, patients, and family members. Rehabilitation services in 12 countries are described in an article that reinforces the need to improve the strategies of rehabilitation services in the face of the challenges posed by the pandemic.[22]

On the rehabilitation of COVID-19 disease, it is known that recommendations for physical therapy treatments in the acute hospital phase exist.[23] However, in addition to respiratory manifestations, neurological complications, the hospitalization period itself generates the need for rehabilitation.[24,25]

The first systematic review on rehabilitation due to the needs arising from COVID-19 indicates that early rehabilitation should be granted to patients hospitalized with the disease; that people with restricted mobility due to quarantine or blockage should receive exercise programs to reduce the risk of frailty, sarcopenia, cognitive decline, and depression, and finally, that telerehabilitation may present as a means of intervention for people who are at home.[26]

Avellanet et al.[27] also report the relevant issue that not only those with sequelae or COVID-19 should be reached for rehabilitation services, but also those with other disabling diseases. Therefore, according to the authors, extensive care for all, i.e., those in isolation or after isolation, is a management challenge. Due to the expertise in intensive hospital rehabilitation modality for several types of patients, as previously mentioned, and the demand to offer proper hospital rehabilitation to patients after COVID-19, the IMREA / Lucy Montoro Rehabilitation Network developed a model of rehabilitation care for those in isolation regime.[21]

Furthermore, given the little scientific information on rehabilitation treatments for patients with COVID-19 in the different phases of the recovery process,[27] we also described the multidisciplinary rehabilitation outpatient model, delivering interventions based on the findings of our evaluations, as previous knowledge may not be the most appropriate in this clinical condition.

OBJECTIVE

This study aims to describe the model of care developed at the Instituto de Medicina Física e Reabilitação do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo for patients with motor, cognitive, psychosocial and nutritional sequelae long after infection by SARS-CoV-2, in an outpatient modality.

METHOD

This study was a retrospective case series without a control group. We retrieved data of patients with a clinically confirmed diagnosis of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection by either polymerase chain reaction (PCR) or serology testing, who received intensive outpatient rehabilitation treatment at IMREA between June 28th and September 14th of 2021.

The inclusion criteria were as follows: age above 18 years; clinically confirmed SARS-CoV-2 infection or confirmed diagnosis of COVID-19 by serology.

Patients with fever for at least three days, requiring antipyretic medications, with mechanical ventilation, chronic kidney disease requiring dialysis, pressure ulcers with the indication of surgical treatment, alternative feeding methods, concomitant treatment for cancer or immunotherapeutic treatments, immunosuppression therapy, clinical instability, unstable mental illness, or active drug addiction were excluded.

This study was approved by the Institutional Review Board of the General Hospital of the Medical College of the University of São Paulo (CAPPesq - Comissão de Ética para Análise de Projetos de Pesquisa), with approval number CAEE 38637620.8.0000.0068.

Assessments

The evaluation protocol for patients with long COVID is consistent with the institutional standards.[28] The sociodemographic and clinical information collected comprises age, gender, ethnic group, education, profession or occupation, origin, body mass index, date of hospital admission, and discharge for the treatment of acute infection. As part of the assessments, information on hospital stay and/or Intensive Care Unit, classification of the severity of SARS-CoV-2 infection by the WHO (Mild, Moderate, Severe and Critical), time since hospital discharge, presence of comorbidities (hypertension, diabetes, obesity, heart disease, vascular diseases, asthma, cancer, or others), time of rehabilitation in outpatient care, and rehabilitation status (objectives achieved, partially achieved or not achieved) were also retrieved.

Clinical and functional assessments

The Functional Independence Measurement Scale (FIM) was administered to evaluate the performance of individuals in the motor and cognitive/social domains. This scale evaluates feeding, personal hygiene, bathing, dressing the upper half of the body, wearing the lower half of the body, toilet use, blatter or bowel management, bed, chair or wheelchair transfers, toilet, bathtub or shower transfer, gait, wheelchair, or stair locomotion, communication understanding and expression, social interaction, problem-solving, and memory.

A person without any disability achieves a score of 126 points, whereas a patient with total dependence should score 18 points, i.e., lower scores stand for more dependence.[29,30]

EQ-5D-5L evaluates the quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. There are five response levels for each of the domains.[31,32]

The World Health Organization Disability Assessment Schedule (WHODAS 2.0) is a generic evaluation tool that cross-culturally provides a standardized method of measuring health and disability. This assessment evaluates the level of functionality of six domains of life: cognition (understanding and communication); mobility (movement and locomotion); self-care (dealing with self-hygiene, dressing, eating, and staying alone); interpersonal relationships (interactions with others); life activities (domestic responsibilities, leisure, work, and school); participation (participate in community and society activities).

WHODAS-2.0 provides a profile and a general measure of functionality and disability that is trans culturally reliable and applicable for all its domains.[33] We used the version with validation for the Portuguese language.[34] Risk stratification was performed according to the World Health Organization model.

The Post-COVID-19 Functional Status Scale (PCFS) measures the functional evolution outcomes in daily life over the post-COVID-19 time. The scale ranges from "0", for the absence of limitations, to “4”, severe limitations of daily life activities.[35]

The Medical Research Council Dyspnea scale (dyspnea MRC) assesses the sensation of dyspnea during activities of daily living. This scale consists of five items ("0" to "4") and the patient should choose the symptoms that correspond to the limitation caused by dyspnea during their daily life.[36]

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale evaluates the state of fatigue, generalized weakness, and tiredness in the previous seven days. This scale is composed of thirteen items, and each item can be scored from "0" to "4".[37]

The Visual Analog Scale (VAS) for pain is a 10 cm straight line on an A4 sheet of paper. On one end, it is written "no pain" and on the other, "worst pain possible". Each patient is asked to mark a sign on the VAS line indicating the intensity of their discomfort or pain. Marks close to the origin (zero centimeters) indicate low pain intensity, and close to the end of the line (10 cm), high pain intensity. The participant should receive an instruction such as "Indicate the amount of pain you experienced in the last 48 hours and make a trace, perpendicular to the line anywhere between "no pain" and "worst pain possible".[38]

The Douleur Neuropathique 4 (DN-4) is a scale that determines the presence or absence of neuropathic pain (≥ 4 points or < 4 points, respectively).[39] It consists of 10 items. Seven of them are associated with the quality of pain (sensory and pain descriptors). The other three are based on clinical examination (hypoesthesia to touch, pins and needles, and allodynia). We used the validated Portuguese version.[39]

The Epworth Sleepiness Scale evaluates the degree of daytime sleepiness. It is a self-applied questionnaire that provides a general assessment of the daytime sleepiness of the subjects evaluated. The questionnaire assesses the probability of napping or falling asleep in 8 day-to-day situations.[40]

The Insomnia Severity Index assesses the current severity of insomnia in the last two weeks in five questions, with answers from "0" to "4".[41]

The Montreal Cognitive Assessment (MoCA) is a brief screening instrument that assesses a wide range of cognitive functions. It measures executive functions, visuospatial abilities, naming, memory retrieval, attention, abstract reasoning, language, and temporal and spatial orientation, necessary to screen for mild cognitive impairment (MCI) and dementia. The application time is approximately 15 minutes,

the maximum score is 30 points, and scores above 26 are considered normal.[42,43]

The Depression, Anxiety and Stress Scale (DASS-21) assessed depression, anxiety, and stress. This scale assesses possible symptoms of anxiety, depression, and stress with 21 questions that rates the participants' experiences during the previous week on a four-point Likert scale of frequency (0- did not apply at all; 1- applied to some degree, or for a short time; 2- applied to a considerable degree, or for a good portion of the time; and 3- applied a lot, or most of the time).[44,45] In addition to being composed of a few items, this scale is easy and quick to administer. Indications of depression, anxiety, or stress are determined by summing the scores, seven items in each domain, multiplied by 2, and ranking them according (Chart 1).

Chart 1. Scores for depression, anxiety, and stress

DASS-21	Normal	Mild	Moderate	Severe	Extremely severe
Depression	0-9	10-13	14-20	21-27	28+
Anxiety	0-7	8-9	10-14	15-19	20+
Stress	0-14	15-18	19-25	26-33	34+

The Functional Oral Intake Scale (FOIS) evaluates oral intake ability at seven levels. The level "1" represents that the patient cannot swallow, and "7" means no swallowing restrictions. It is a simple scale that allows the rapid detection of difficulties in oral feeding.[46]

The Ambulatory Nutritional Screening Protocol included current bowel habit, frequency of bowel movements, consistency of feces classified according to the Bristol Fecal Scale, presence of exertion bowel movements, bleeding, presence of hemorrhoids, and use of laxatives.[47] Patients were also asked about their personal and family history. Assessment of current eating habits consisted of food groups, volume, and fractionation.[48]

Instrumentalized assessments

Medical Research Council sum score (MRC)[49] evaluates the muscle strength of twelve muscles they perform on each side of the body: right arm abduction, right forearm flexion, right wrist extension, right hip flexion, right knee extension, right ankle dorsal flexion.

The degree of muscle strength varies from "0" complete paralysis; "1": minimal contraction; "2": absence of active motion against gravity; "3": weak contraction against gravity; "4": active movement against gravity and resistance; "5": normal strength.[49]

Timed Up and Go Test (TUG): Consists of measuring, in seconds, the time spent by the individual to get up from the chair, walk three meters, return and sit back in the chair. The test is repeated three times, being selected the shortest time of the individual.[50]

The 10-minute Walking Test (10-MWT) evaluates the short-term walking speed. It is recommended that the individual walks 14 meters through, disregarding the initial and final 2 meters. The patient should walk at his normal speed.[51]

In the 1-minute Sit-to-Stand Test (1-MSTST), the patients are requested to stand and sit on a chair approximately 43cm centimeters high, without an armrest, as fast as they can, for one minute.[52] This test should be conducted if oximetry measurement is above 90%.

The Borg Dyspnea Scale assesses the degree of dyspnea in categories "0" no up to "10" maximum at rest and after the 1-minute Sit-to-Stand Test.[53,54]

The Handgrip evaluates muscle strength using a dynamometer to measure the maximum force produced during a five-toed grip. Three trials were performed on each side, with the average of the strongest side being computed. Patients were seated, the arm next to the body, elbow at 90 degrees, neutral forearm, and the wrist slightly extensive.[55,56]

The Body Mass Index (BMI) of the patient was calculated using the Quetelet formula: Current weight (Kg) / height² (m). The BMI value was classified according to the cutoff points for adult and older populations determined by the World Health Organization and Pan-American Health Organization (PAHO), respectively.[57,58]

Body composition was performed by Dual Energy X-ray Absorptiometry data (LUNAR® DPX NT system, Apodaca, Mexico): percentage of lean mass (%), fat percentage (%), resting metabolic rate (cal/day), relative skeletal muscle index (kg/m^2) which corresponds to lean arm mass (kg) + lean leg mass (kg)/height^2 (m).

Isokinetic strength and total work was evaluated with by HUMAC® Cybex Norm (Computer Sports Medicine Inc, Stoughton, USA): Bilateral peak torque for knee extensions per body weigth and bilateral total work per body weight.

The muscle thickness of the right *vastus intermedius* and *rectus femoris* were measured with FujiFilm SonoSite® M-Turbo (Bothell, Washington, USA). The transverse cut image was performed at the lower and medial third intersection between the anterosuperior iliac spine and the upper edge of the right patella. The patient lay with the leg in a neutral and relaxed position, and a linear transducer of 13Hz and depth of 6 to 10cm was used in this evaluation.

Finally, after a detailed cardiac evaluation and consequent medical approval, the patients were released to begin the outpatient rehabilitation program. The evaluations were conducted at baseline, between five and seven days after the sixth treatment session, and at discharge.

Outpatient Rehabilitation Program

The optimized and short-term multidisciplinary intensive rehabilitation strategy of the Institute of Physical Medicine and Rehabilitation (IMREA) consisted of weekly visits, administered twice a week, carried out by specialized professionals of Physiotherapy, Occupational Therapy, Physical Conditioning, Psychology, Nutrition, and Medical and Dental Services, when applicable. Six sessions of 30 to 40 minutes of each composed the rehabilitation program, according to the individual functional needs and the multidisciplinary evaluations.

Medical treatments

After evaluating clinical and functional parameters, and the result of complementary tests, if there was pain in the locomotor system, the interventions listed below were employed, according to a hierarchical scheme.

Radial shock waves: This intervention consisted of the application of 2,000 radial shock wave impulses through a pneumatic generator, Swiss DolorClast® (EMS Electro Medical Systems, Nyon, Switzerland), with the Power® handpiece, at a frequency of 15-20Hz, and with individual acoustic pressure of 2.5 to 4.0 bar. This setup allowed the energy flow density of

0.10 to 0.16mJ/mm2, and it was applied according to the patient's pain tolerance. The application site was the most painful site on palpation of the affected structures, and this intervention was conducted for three weeks.[59]

Focal shock waves: The treatment was delivered through an electromagnetic generator Duolith Ultra SD1 (STORZ Medical, Tagerwillen, Switzerland). According to the painful structure, the focal shockwave was set to reach between 1.5 and 5.0 cm depth and deliver up to 2000 pulses per treated segment. The sessions were conducted once a week for four consecutive weeks.

We evaluated muscle contraction response parameters in a hierarchical regime for patients with minial pain or after the pain treatment.

The muscle strength for extending both knees was measured individually for each muscle (*vastus medialis, vastus lateralis, rectus anterior*, and *vastus intermedius* of the quadriceps muscle). This assessment used ultrasound-guided electrical induced muscle contraction.

The stimulation parameters followed physiological data according to muscle fibers composition.[60-62] The frequency of electrical stimulation was based on the recruitment of muscle fibers in the different muscles:

1. Evaluation of aerobic, type I muscle fibers, of slow contraction, high mitochondrial density, high oxidative capacity, and high fatigue resistance: electrical stimuli with 20 Hz.[60-62]

2. Evaluation of anaerobic type IIb muscle fibers, of very fast contraction, low mitochondrial density, high glycolytic capacity, and little resistance to fatigue: electrical stimuli with 60 Hz.[60,62] This assessment was conducted if there was no contraindication for electrical or magnetic stimulation, such as a pacemaker or metal implant.

Evaluation of electrically induced muscle contraction

A ultrasound system evaluated the right *rectus femoris* and *vastus intermedius* muscles at rest and during electrically induced muscle contractions. Peripheral inductive magnetic electrostimulation by Super Inductive System® (BTL, Czech Republic) was used according to Paolucci et al.[63] to obtain muscle contractions rated as:

- No visible muscle contraction;
- Visible muscle contraction, without joint movement;
- Visible muscle contraction, with knee extension that overcomes gravity, without external load;
- Visible muscle contraction, with knee extension that overcomes gravity, with progressive external load;
- A muscle contraction with knee extension that overcomes the external load of 10% of body weight.

We calculated the maximum load for quadriceps from the peak torque measured at the isokinetic dynamometer, and this load matched 40% of the peak knee extensor torque.[61]

The quadriceps muscle contraction assessment was induced by neuromuscular electrical stimulation by the RECARE® system (Visuri, Brazil). The 9x5cm electrodes were positioned on the *vastus medialis* and *vastus lateralis*, and a neutral electrode was placed at the root of the thigh of the *recuts femoris* muscle (Figure 1).

The stimulation begun after mapping and placing the electrodes on specific sites to obtain the best muscle contraction, according to the parameters of electromagnetic stimulation. Such assessments were repeated in the *gluteus maximus* and *medius*, *tibialis anterior*, thoracic paravertebral, *supraspinatus*, and *infraspinatus* muscles. Patients with contraindication to electrical or magnetic stimulations were prescribed isokinetic dynamometer training, performed twice a week.

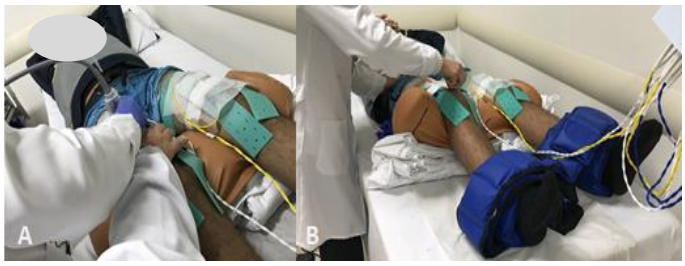

Figure 1. Evaluation of electrically induced muscle contraction by electrical stimulation (RECARE® system) in the *vastus lateralis* and *vastus medialis* muscles, under ultrasound guidance without (A) and with progressive external load (B)

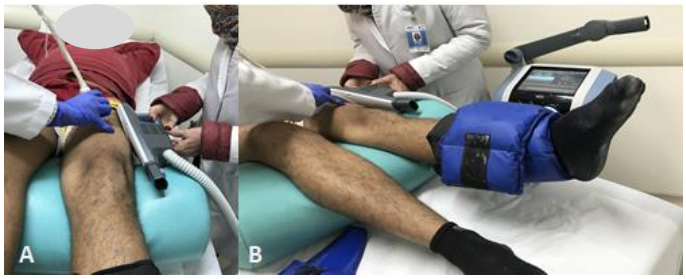

Figure 2. Assessment of electrically induced muscle contraction using the peripheral inductive magnetic electrostimulation over in the quadriceps muscle without (A) and with external load (B)

Physiotherapy

According to the electrically induced muscle contraction results, an electrically induced muscle strengthening program was initiated. These programs were composed of peripheral inductive magnetic electrostimulation and neuromuscular electrical stimulation.

Peripheral inductive magnetic electrostimulation

Three consecutive sections were planned, with a total treatment time of 13 minutes in each limb, with an inductive magnetic eletrocstimulation by Super Inductive System® – SIS 6000 (BTL, Czech Republic) as described by Paolucci et al.[63] This system uses a 2.5 Tesla focal field, inducing a myomotor current of 10 cm deep. All muscle groups described above were mapped.

The estimated total therapy time, including positioning and mapping, was 30 minutes for both quadriceps. In each session, patients were placed supine with 30° of knee flexion over a cushion (Figure 2).

The stimulation parameters were: 5 seconds stimulus followed by another 5-second pause. This sequence was repeated for three frequencies, 8Hz for one minute, 20 Hz for six minutes, and 60 Hz for another six minutes.

The maximum output power was 100% at 8 and 20 Hz and 52% at 60Hz. Rapid mapping of the most effective stimulation point was performed to obtain the best muscle contraction.

Other antigravitational and muscle groups stabilizers were mapped at the trunk and upper limbs.

The peripheral inductive magnetic electrostimulation program was performed on an outpatient basis twice a week until effective muscle contraction with an external load of 10% of body weight was obtained.

When muscle response was absent or reduced, neuromuscular electrical stimulation by RECARE® (Visuri, Brazil) was performed.

Neuromuscular electrical stimulation

Neuromuscular electrical stimulation using the RECARE® system (Visuri, Brazil), with 9x5cm electrodes were positioned over the *vastus medialis* and the *vastus lateralis* muscles. The neutral electrode was placed at the root of the thigh over the *rectus anterior* muscle after mapping to the optimal sites to obtain the best muscle contraction.

Electrodes of the 9x5cm were positioned on the gluteus medius and maximus, thoracic paravertebral (T6-T12), and infraspinatus muscles over the muscle belly. Also, a 5x5cm electrode was applied to the tibialis anterior and supraspinatus muscles over the muscle belly.

The following stimulation parameters were used: ascent time: 0 seconds; descent time: 1.0 second; duration of stimulation time: 5 seconds; duration of rest time: 10 seconds; pulse width: 500 microseconds; stimulation frequency: 20 Hz; stimulus intensity (milliamperes): according to the patient's tolerance and progressive external load. The session lasted 45 minutes and was conducted twice a week, until discharge criteria were achieved. In cases of contraindication to electrical or magnetic stimulation, such as a pacemaker or metal implant, and for patients with peak torques below 1 Nm/kg, isokinetic strengthening training of knee flexion and extension were prescribed. The intervention was conducted at speeds of 60° and 180° per second, twice a week, until reaching relative knee extension torque above 1 Nm/kg.[64]

Psychology

The psychology service evaluated the patients individually, according to the instruments described in a 30-minute session. According to the results of the MoCA instruments, for screening cognitive functions and DASS-21, for the evaluation of symptoms of anxiety, depression, and stress, they were referred for treatment in the psychology service for emotional approach (if DASS-21 ≥ moderate) and cognitive stimulation (in cases of MoCA score <26).

Patients who went through the psychology service for intervention were submitted to sessions twice a week for three weeks, totaling six intervention sessions of 30 minutes each, with structured interventions divided:

Emotional intervention with the psychoeducation technique (for 15 minutes), each session with a different theme about psychological and cognitive sequelae after COVID-19 infection; and cognitive training (for 15 minutes) through the NeuronUp Cognitive Stimulation Platform (NeuronUp®)[65] always being the same three tasks (5 minutes each), with difficulty level adaptable to each patient according to performance.

Psychologists from the institution's team mediated all intervention sessions. The psychoeducation technique was used for an emotional approach, an evidence-based practice developed professionally that integrates psychotherapeutic and educational interventions. It can be defined as teaching the patient relevant psychological knowledge and principles.[66]

Psychoeducational themes were selected by the psychology team, with appropriate content and theoretical basis, on the topics: "Psychological and cognitive sequelae post COVID-19", "Posttraumatic stress", "Depression" and "Anxiety".

The digital computerized cognitive stimulation platform NeuronUp® (neuronup.com.br)[65] was used for cognitive intervention. This is an online neurorehabilitation platform composed of different resources addressed to psychologists to help them design cognitive rehabilitation interventions.[65]

The materials are based on the ecological validity concept. According to this concept, the skills trained and improved during the rehabilitation sessions must transform into improvements in daily activities. In other words, the intervention focusing on the generalization that the results obtained during training should also be evident in other similar real-life environments.

The training protocol started at the minimum level of difficulty for all participants, in each domain and according to the patient's performance in each task. The program was set as follows:

1. Sort Sequences: Sort a series of previously memorized visual elements (visual and related elements, fixed memorization time, and immediate playback), demanding episodic memory training.

2. Balances Bags: Knowing the weight of the different products, placing them in bags balancing the weight between both arms, demanding work memory training, flexibility, planning, and reasoning with calculation.

3. Select Elements of a Category: Select a series of objective elements from a requested category, from a group of distracting stimuli, demanding selective attention training and semantic memory.

Finally, patients were reevaluated by the psychology service, according to the exact assessments described in a 30-minute session.

Nutrition

Two to three individual visits lasting one hour were delivered to promote autonomous and voluntary healthy eating habits. These included ingestion of fruits and vegetables suitable for different ages, preference of fresh rather than industrialized foods, increased consumption of low glycemic carbohydrates, and lean sources of proteins of high biological value. Attention was given to the local food pyramid guides. When appropriate, specific eating guidelines for diabetes mellitus, systemic arterial hypertension, dyslipidemias, constipation, and bone health were addressed.[67]

Nursing

According to the results of the evaluations by the Epworth sleepiness and severity of insomnia scales, sleep guidance videos prepared by the nursing service were presented.

Occupational Therapy

According to the functionality evaluation results for upper limbs and degree of functional independence, the intervention

was conducted to improve performance in basic and instrumental activities of daily living, education, work, and leisure. Also, the occupational therapy sessions delivered training to prevent imbalances in occupational areas through graduation and adaptation of tasks and improvement of upper limbs and praxis motor skills.

According to individual needs, environmental barriers limiting the person's autonomy were evaluated, and adaptations were proposed. The needs of assistive technology were also evaluated to promote functional independence and greater participation in the performance of tasks, increasing engagement in significant activities and resumption of occupational roles.

Educational program

The educational program is available at the app COMVC.[68]

Discharge criteria for outpatient rehabilitation treatment

The discharge criteria are listed below:

1. Pain intensity < 4 at a visual analog scale (VAS);
2. Electrically induced extension of the knee in supine position with 30° knee flexion capable of overcoming the resistance of 10% of the bodyweight;
3. Electrically induced muscle contraction against gravity in *gluteus maximus* and *medius, tibialis anterior*, thoracic paravertebral, *supraspinatus*, and *infraspinatus*;
4. Criteria of psychological evaluation: clinical evaluation of complaints and test results, follow-up of the guidelines provided, and reports of patient well-being.

Data analysis

Data consisted of records collected as repeated measures at four time points: T0= median of 14.32 (14.00; 14.67) months alter hospital discherge, T1= baseline, T2= 6 sessions, and T3= post-intervention. Only T1 and T3 were available for analysis for some of the evaluations. Descriptive statistics are presented as median (interquartile range) for continuous variables or absolute and relative frequency for categorical data.

Four evaluations were selected as the primary outcomes of interest, prior to data analysis, based on previous findings and literature reports: PCFS, VAS for Pain, Handgrip Strength, and TUG test. This choice was made to prevent multiple testing on the small sample of patients available. Tests of difference among the repeated measures were carried out on those four variables only. They were performed using the non-parametric Friedman Test, with Fisher's Least Significant Difference as post-hoc.

The remaining continuous or ordinal variables were evaluated with simple Linear Regression with an Ordinary Least Squares method to estimate unknown parameters. A different model was adjusted for each patient on each variable, allowing for patient-specific slopes and intercepts similar to a Linear Mixed Effects model with no interaction terms.

Finally, the patients' slopes were averaged for each variable, and a 95% confidence interval was constructed based on two-tailed T-Tests. A Mixed Logit Model with the patients' ID as Random Effects was carried out for the categorical variables. The Fixed Effect was whether the rehabilitation had already started (T2, T3) or not (T0, T1).

Although individual patient effects were considered, we did not control for specific confounders such as age, sex, or race due to the small sample size. The family-wise error rate was controlled for with the Holm-Bonferroni adjustments. Results are considered significant for corrected p-values < 0.05. The analyses were carried out using Python, IBM SPSS Statistics 27, and R Studio.

RESULTS

This study included 13 patients. One patient was excluded from the analysis due to an associated arterial vascular condition under investigation. Our sample included six men and six women (50% each). Sociodemographic characteristics of the included patients are presented in Table 1.

Table 1. Sociodemographic and clinical characteristics

Variable	Median (Interquartile Range)
Age, years	59.00 (52.50; 69.25)
Lenght of hospital stay, days	17.50 (12.75; 22.00)
ICU Length of Stay (n= 11) days	9.00 (5.50; 12.00)
Intubation period, days	8.00 (5.50; 16.00)
Time since hospital discharge, months	14.32 (14.00; 14.67)
Outpatient rehabilittation duration, days	57.50 (51.50; 61.00)
Body Mass Index (BMI)	29.20 (27.52; 34.22)
BMI category, (%)	
Normal	1 (8,3%)
Overweight	6 (50%)
Obese	5 (41.7%)
Fat percentage, (%)	41.15 (36.25; 42.1)
Lean mass percentage, (%)	57.35 (56.12; 61.67)
RSMI, kg/m²	8.58 (7.74; 8.92)
Android/gynoid	1.1 (1.06; 1.32)
Visceral fat, (kg)	1.78 (1.46; 2.10)
Subcutaneous fat, (Kg)	1.42 (1.10; 1.75)
Resting metabolic rate, (cal/day)	1.527 (1,362.25; 1.636.75)
Variable	**Count (% of total)**
Self-Reported Race	
Black	2 (16.67%)
Mixed Ancestry	6 (50.00%)
White	3 (25.00%)
Indigenous	1 (8.33%)
Education Degree	
Never attended school	1 (8.33%)
Incomplete primary education	3 (25.00%)
Complete primary education	2 (16.67%)
Incomplete secondary education	1 (8.33%)
Complete secondary education	5 (41.67%)
Job status post-Covid	
Yes, in person	4 (33.33%)
Unable to return to work	2 (16.67%)
Lost the job for the pandemic	1 (8.33%)
Does not work/retired	5 (41.67%)
Comorbidities	
Hypertension	9 (75.00%)
Diabetes	4 (33.33%)
Renal Failure	1 (8.33%)
Hematological Disease	1 (8.33%)
Cancer	1 (8.33%)
ICU Stay	11 (91.67%)
Intubation	9 (75.00%)
WHO COVID-19 Severity Classification	
Critical	9 (75.00%)
Severe	3 (25.00%)

Legend: *ICU= intensive care unit; RSMI= Relative Muscle Index*

Complete functional assessments at T0, at baseline (T1), between five and seven days after the sixth treatment session (T2), and at discharge (T3) are displayed (Table 2). The median rehabilitation duration was 57.50 (interquartile range: 51.50; 61.00) days, with a minimum of 21 days and a maximum of 78 days.

Table 2. Functioning assessements

Variable	Values presented as Median (Interquartile Range)			
	T0	T1	T2	T3
TUG Test (s)	11.98 (10.04; 14.48)	12.59 (9.46; 14.93)	11.57 (9.88; 12.92)	9.36 (8.77; 11.70)
Handgrip Strength Test (Right Side)	17.83 (15.92; 23.17)	24.83 (16.92; 29.50)	23.83 (17.83; 28.92)	26.33 (19.50; 35.17)
Handgrip Strength Test (Left Side)	14.65 (12.83; 23.00)	23.00 (18.17; 28.58)	22.67 (17.25; 28.42)	26.33 (20.75; 32.08)
10-Meter Walking Test (s)	13.10 (12.28; 15.48)	9.43 (7.88; 11.22)	9.57 (8.95; 10.73)	8.62 (7.94; 9.46)
Epworth Sleepiness Scale	11.00 (4.75; 15.25)	7.50 (2.00; 16.25)	14.50 (7.75; 16.50)	9.00 (4.75; 12.75)
Insomnia Severity Index	9.50 (4.50; 12.25)	11.00 (5.50; 13.00)	11.00 (5.75; 13.50)	7.50 (5.75; 9.50)
FIM	111.50 (108.00; 118.00)	109.50 (104.50; 124.00)	117.50 (115.75; 120.25)	114.50 (110.50; 120.50)
WHODAS-2.0	18.00 (14.00; 24.25)	18.50 (16.75; 26.50)	18.50 (15.75; 30.25)	15.00 (13.00; 25.00)
PCFS	1.00 (0.75; 1.00)	2.00 (1.75; 2.00)	1.50 (1.00; 2.00)	1.00 (0.00; 2.00)
FACIT	14.50 (10.25; 20.00)	13.50 (10.25; 24.00)	13.00 (9.00; 21.00)	8.50 (6.75; 15.50)
MRC Dyspnea Scale	1.00 (1.00; 1.25)	1.00 (1.00; 2.00)	1.00 (0.00; 1.00)	1.00 (1.00; 1.00)
VAS for Pain (Right Side)	39.50 (30.00; 67.50)	23.50 (0.00; 57.50)	45.00 (22.50; 52.50)	0.00 (0.00; 2.00)
VAS for Pain (Left Side)	59.50 (27.00; 88.00)	42.00 (8.00; 70.00)	45.00 (0.00; 70.00)	0.00 (0.00; 1.25)
Rectus Femoris Thickness (cm)	1.17 (1.08; 1.22)	1.33 (1.12; 1.40)	1.40 (1.34; 1.55)	1.43 (1.32; 1.49)
Vastus Intermedius Thickness (cm)	1.27 (1.00; 1.44)	1.27 (1.14; 1.43)	1.45 (1.29; 1.61)	1.35 (1.25; 1.67)
EQ-5D-5L (mobility)	1.00 (1.00; 3.00)	2.00 (1.00; 3.00)	2.00 (1.00; 2.00)	1.00 (1.00; 2.00)
EQ-5D-5L (self-care)	1.00 (1.00; 1.25)	1.00 (1.00; 2.00)	1.50 (1.00; 2.00)	1.00 (1.00; 1.00)
EQ-5D-5L (daily routine)	1.00 (1.00; 2.25)	2.00 (1.00; 3.00)	2.00 (1.00; 2.00)	1.00 (1.00; 1.25)
EQ-5D-5L (pain and discomfort)	3.00 (1.00; 4.00)	2.00 (2.00; 3.00)	2.00 (2.00; 3.00)	2.00 (1.00; 2.00)
EQ-5D-5L (anxiety and depression)	2.00 (1.75; 3.00)	1.50 (1.00; 3.00)	1.00 (1.00; 2.25)	1.50 (1.00; 3.00)
EQ-5D-5L (Visual Analog Scale)	77.50 (60.75; 86.25)	80.00 (50.00; 81.25)	80.00 (75.00; 90.00)	92.50 (90.00; 100.00)
Medical Research Council sum score	56.00 (53.50; 59.00)		60.00 (57.75; 60.00)	60.00 (58.00; 60.00)
FOIS	7.00 (7.00; 7.00)	7.00 (7.00; 7.00)	7.00 (6.50; 7.00)	7.00 (7.00; 7.00)
MoCA		18.00 (13.75; 24.00)		22.00 (16.50; 24.00)
1-MSTST		12.00 (9.75; 17.75)		16.50 (14.00; 19.25)
Borg Scale Pre		1.75 (0.00; 3.89)		0.75 (0.00; 2.25)
Borg Scale Pos		5.50 (3.00; 7.00)		2.00 (1.75; 6.00)
Rigth Peak Torque Extensors / Bodyweight		0.67 (0.44; 0.82)		0.67 (0.59; 0.76)
Left Peak Torque Extensors / Bodyweight		0.63 (0.34; 0.93)		0.71 (0.51; 0.89)
Right Total Work Extensors / Bodyweight		5.23 (2.55; 8.60)		5.96 (4.29; 7.06)
Left Total Work Extensors / Bodyweight		5.74 (1.96; 8.71)		7.51 (2.01; 9.35)
Variable	**Values presented as count (% of total)**			
	T0	**T1**	**T2**	**T3**
DASS-21 - Anxiety				
Normal		6 (50.00%)		8 (72.73%)
Mild		1 (8.33%)		0 (0.00%)
Moderate		2 (16.67%)		1 (9.09%)
Severe		1 (8.33%)		0 (0.00%)
Extremely Severe		2 (16.67%)		2 (18.18%)
DASS-21 - Depression				
Normal		10 (83.34%)		8 (72.73%)
Mild		0 (0.00%)		2 (18.18%)
Moderate		1 (8.33%)		0 (0.00%)
Severe		0 (0.00%)		0 (0.00%)
Extremely Severe		1 (8.33%)		1 (9.09%)
DASS-21 - Stress				
Normal		8 (66.66%)		8 (72.73%)
Mild		0 (0.00%)		0 (0.00%)
Moderate		2 (16.67%)		2 (18.18%)
Severe		2 (16.67%)		0 (0.00%)
Extremely Severe		0 (0.00%)		1 (9.09%)

Legend: *T0= median of 14.32 (14.00; 16.67) months after hospital discharge; T1= baseline; T2= 6 sessions; T3= post-intervention*

Each of the non-categorical evaluations' score progression, along the different times, may be analyzed using the average slopes reported in Table 3. Confidence intervals are computed with two-tailed t-Tests.

Table 3. Average of patient slopes computed for each continuous or ordinal variable, along with the standard deviation

Variable	Average Slope	S.D. Slope	95% C.I. Lower	95% C.I. Upper
TUG Test*	-0,85	0,931	-1,468	-0,232
Handgrip Strength (Right Side)*	1,82	2,122	0,412	3,229
Handgrip Strength (Left Side)*	2,309	1,962	1,007	3,611
10MWT*	-1,524	0,777	-2,04	-1,009
1-MSTST	2.667	4.308	-0.192	5.525
Epworth Sleepiness Scale	0,408	2,304	-1,121	1,937
Insomnia Severity Index	-0,175	1,769	-1,349	0,999
Functional Independence Measure*	1,35	1,7	0,222	2,478
WHODAS-2.0	-0,4	2,249	-1,893	1,093
PCFS	-0,075	0,28	-0,261	0,111
FACIT - Fatigue Scale	-1,242	2,559	-2,94	0,457
MRC Dyspnea Scale	-0,108	0,317	-0,319	0,102
VAS for Pain (Right Side)*	-12,943	9,185	-19,038	-6,848
VAS for Pain (Left Side)*	-16,59	12,024	-24,57	-8,611
Rectus Femoris Thickness (cm)*	0,09	0,065	0,047	0,133
Vastus Intermedius Thickness (cm)	4,985	16,365	-5,875	15,845
EQ-5D-5L (mobility)	-0,1	0,398	-0,364	0,164
EQ-5D-5L (self-care)	-0,083	0,227	-0,234	0,067
EQ-5D-5L (daily routine)	-0,058	0,355	-0,294	0,177
EQ-5D-5L (pain and discomfort)	-0,258	0,439	-0,549	0,033
EQ-5D-5L (anxiety and depression)	-0,158	0,352	-0,392	0,075
MRC	0,887	1,447	-0,073	1,847
MoCA	1.455	2.675	-0.43	3.34
DASS-21 Anxiety*	-2.182	2.48	-3.929	-0.435
DASS-21 Depression	-2.727	4.454	-5.865	0.411
DASS-21 Stress	-3.273	6.621	-7.938	1.392
Cybex MID	-0.126	0.221	-0.306	0.055
Cybex MIE	0.04	0.2	-0.123	0.203

Legend: *S.D.= Standard Deviation; C.I.= Confidence Interval; TUG= Timed Up and Go; 10MWT= 10-Meter Walking Test; 1-MSTST=1-Minute Sit-to-Stand Test; WHODAS= World Health Organization Disability Assessment Schedule 2.0; PCFS= Post-Covid-19 Functional Status; FACIT-Fatigue; Functional Assessment of Chronic Illness Therapy Fatique Scale; MRC= Medical Research Council; VAS= Visual Analog Scale; MoCA= Montreal Cognitive Assessment; DASS-21= Depression, Anxiety and Stress Scale*

Examples of how the average slope relates to each patient progression can be seen in the plots present in Figure 3. The average slope (inclination) relates to the overall performance of the patients. The green line represents the average regression line, and the multicolored dots with connecting lines, individual patient measurement.

Note that, on average, many of the evaluations presented slopes in the direction of improvement for the patient, e.g., the average slope for the TUG Test is negative, indicating that the patients tended to take less time to complete the test as the rehabilitation program progressed. However, one should also consider the 95% confidence interval calculated for each slope. If this interval includes zero, it is less evident in which direction the variable is progressing, or even if it is indeed progressing. Thus, the primary outcomes from Table 3 are those in which the 95% confidence interval for the mean does not cross zero. Those variables are marked with an asterisk.

A clear tendency of improvements is observed in TUG test (as commented above) and the 10MWT. Both assessments present a trend of reduction in the test completion time.

Handgrip strength of both hands and the FIM scores also presented a strong trend of improvement (better scores a times progressed). As measured with the DASS-21 anxiety also tended to improve, with the patients scoring lower on latter times.

Ultasound (US) analyses of muscle thickness width detected a trend of improvement for the *rectus femoris*, albeit with a very low coefficient. The *vastus intermedius*, on the other hand, did not present any clear trend. Those results were fitted with a Mixed Logit Model. Although the slopes were negative on both muscles, neither reached a statistically significant coefficient (p= 0.078 for *rectus femoris* and p= 1.00 for *vastus intermedius*).

By and large, the most significant effect we observed in our results is the reduction of pain intensity measured by the VAS. Pain on both sides tended to decrease with a steep negative slope. Interestingly, the EQ-5D-5L Pain and Discomfort subdomain has also decreased the score, however the confidence interval for the β coefficient included zero.

In subsequent analysis, the VAS for pain, handgrip strength, TUG, and PCFS were tested with Friedman's Test for differences in the repeated measures. In those tests, we have used a summary score for the VAS and handgrip strength variable, in which only the largest value from either side was considered. Therefore, we compared the patient's strongest side and the most affected side by pain at each time point. The results are summarized in Table 4. Post-hoc tests were performed only when the primary test reached significance.

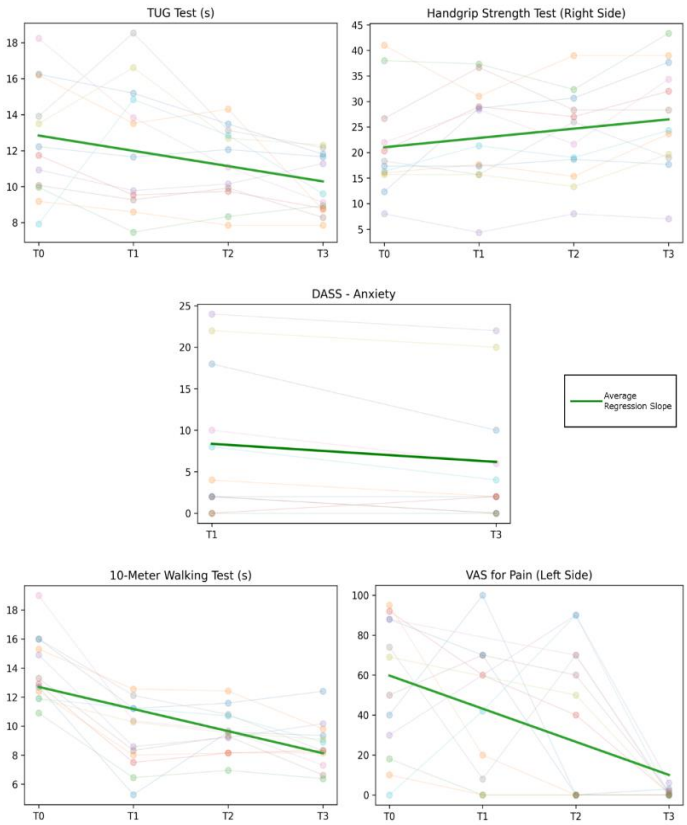

Figure 3. Plots showing the average regression line and the individual patients' evaluations across the repeated measures times

Table 4. Results for the Friedman's Test for difference in repeated measures. Fisher's LSD post-hoc tests were performed when significant differences were found

Variable	Friedman's Test p-value	Fisher's LSD post-hoc p-value					
		T0 - T1	T0 - T2	T0 - T3	T1 - T2	T1- T3	T2 - T3
PCFS	0.068						
Handgrip Strength	0.068						
VAS for Pain	0.015*	0.001*	0.002*	<0.001*	0.322	0.032*	0.002*
TUG	<0.001*	0.029*	0.015*	<0.001*	0.777	0.054	0.097

Legend: *LSD= Least Significant Difference; T0= median of 14.32 (14.00; 16.67) months after hospital discharge; T1= baseline; T2= 6 sessions; T3= post-intervention; PCFS= Post-Covid-19 Functional Status; VAS= Visual Analogue Scale; TUG= Timed Up and Go*

Although no statistically significant difference was found in PCFS and handgrip strength, the p-values obtained indicate that those differences may be a trend. Nevertheless, VAS for Pain and TUG tests had significant differences in their measurements time.

With the post-hoc tests, one can see that, for both variables, the most significant differences occur when comparing any measurement with T3, which is at the end of the rehabilitation program. This finding is especially notable for VAS, corroborating what was found through the slope analysis.

Patients were discharged from the outpatient rehabilitatin program with objectives achieved, within a median of 57.50 (interquartile range: 51.50; 61.00) days.

DISCUSSION

Even 14 months after hospital discharge, all patients evaluated still presented long COVID related symptoms and functional disability and therefore required a customized rehabilitation program. The optimized and intensive model of short-term outpatient care of patients with long COVID reduces the symptoms of pain and improves mobility.

We observed a clear, not statistically significant trend of improvement in the PCFS, FIM, handgrip strength, 10-Meter Walking Test and DASS-21 anxiety.

We justified this trend by the small number of subjects included in this study. On the other hand, the statistically significant improvement in bilateral VAS for pain and TUG values suggests greater effects on pain and mobility variables.

These findings were observed as the results of an intensive, integrated, and coordinated multidisciplinary team approach, intervening interdisciplinary. The number of sessions and therapies varied according to the patient's individual rehabilitation needs. All patients were discharged with goals achieved after a median of 57.50 days.

Despite the patient's reports and the multidisciplinary team's findings of clinical improvement, our intervention did not influence the results indicated in the scales of daytime sleepiness, insomnia, depression, stress, and cognitive aspects, such as attention, memory, and executive functions.

The Timed Up and Go test is a valuable predictor of the risk of falls.[69] It has been used in several populations with and without disabilities.[70-74] Reference values vary from age groups and populations,[75,76] however, robust data on long COVID patients hospitalized due to moderate or severe COVID-19 is still limited in the literature.

Significant improvements in TUG values obtained after our short, optimized outpatient rehabilitation program, even within a few patients, highlighted the relevance and the need for instrumentalized assessments to document its impact. TUG may influence future functional outcomes, as it helps assess balance variables.[77] All patients had chronic pain. The pain was nociceptive and nociplastic, predominantly.[78] However, we observed two cases of neuropathic pain. One patient was excluded from the analysis due to an associated arterial vascular condition under investigation. Joint and muscle pain is a common sequela in long COVID patients after hospital discharge.[78-80]

Similar to the evidence related to the benefits of the interdisciplinary approach to the expressive improvement of chronic pain symptoms, it can be inferred that in the case of patients after COVID-19, the same phenomenon occurred. The treatment instituted with radial or focal extracorporeal shock waves was performed according to the evaluation of the affected structures and better therapeutic indication. The main structures affected were the knees, shoulders, and lumbar spine.

We observed that pain management and inflammatory control with focal extracorporeal shock waves prior to muscle strengthening procedures reduced reflex inhibition and promoted tolerance to electrical stimulation and adherence to treatment to achieve the functional goal. One patient had infraspinatus muscle insertion enthesopathy and chronic pain in the posterior region of the shoulder, probably due to the repeated pronation position during the ICU stay.

Reduced response to electrostimulation electrical stimulation was observed in several muscle groups in all patients. The main muscles affected were the quadriceps, the gluteus maximus and medius, tibialis anterior, hamstrings, thoracic paravertebral, supraspinatus, and infraspinatus, symmetrically. We only assessed the main antigravitational and girdle stabilizer muscles. We cannot infer that other muscles were similarly affected.

Our stimulation parameters followed physiological data based on different components of the skeletal muscle fibers. Mapping of these structures demonstrated absence or lack of electrically induced contractions at 20Hz, indicating the involvement of aerobic, type I muscle fibers.[60,62,81] This finding is also observed in ten patients with chronic fatigue syndrome.[82] Compared with healthy controls, Pietrangelo et al.[82] identified a significant transformation from aerobic into anaerobic muscle fibers.

These changes were detected in the biopsy of the *vastus lateralis* muscle in a period of five to 7.8 years of disease compared with healthy controls.[82]

Possible molecular mechanisms may be related to the genetic expression of acetylcholine receptors. This issue may reduce the efficiency of neuronal transmission at the neuromuscular junction of the repetitive low-frequency firing of motoneurons essential for slow-fiber-type.[82] These mechanisms may not translate into structural modifications of muscle fibers detectable in imaging tests. We could not detect changes in muscle thickness captured in ultrasonography at least 14 months after the SARS-Cov-2 infection. Similarly, one should not expect the improvement of isokinetic maximum muscle strength, which recruits predominantly type II fibers. The effects of isokinetic resistance training should be then considered in long COVID patients.

It is essential to emphasize that the histological analysis in COVID-19 cadavers shows predominant type II muscle fibers.[83] In these acute cases, the effect of COVID-19 on the biopsy findings cannot be isolated or underestimated. It is essential to consider that cases of immobility and sarcopenia in the elderly also deplete, preferably, type II anaerobic fibers. However, we found the reduced or absence of contraction of type I muscular fibers response to electrical stimulation in one year. In spinal cord injury patients, there is also the transformation of muscle fibers, characterized by the loss of type I, aerobic with the increase of type IIa, during the first year of spinal cord injury evaluated in a biopsy of the vastus lateralis muscle in twelve patients.[84]

Thus, we highlight the importance of understanding the dynamic composition of physiological and pathological fibers in each muscle structure and its evaluation for the use of the best therapeutic stimuli. We did not find previous reports on the most affected types of muscle fibers in long COVID patients. Although the physiological composition of muscle fibers varies among different groups,[85] during the natural sequence of motor activation, in general, type I muscle fibers are recruited first.

The activation occurs at low intensities of efforts, usually up to 25% of maximum muscle strength, allowing the long-term aerobic activity.[86] By increasing external resistance, type II fibers of greater muscle volume are recruited, capable of developing greater strength, but have little resistance and can sustain activity for short periods and use immediate reserves such as ATP-CP and anaerobic glycolysis. Therefore, we hypothesize that due to a possible reflex inhibition mechanism and the possible selective neuromuscular block of type I muscle fibers in long COVID patients, type II fibers are early activated, reducing the ability to maintain prolonged efforts and causing fatigue.

We emphasize that there was not enough time to transform the morphological composition of muscle fibers during the outpatient rehabilitation program, as described in cases of long evolution in spinal cord injury[82] and chronic fatigue.[81] The short duration of treatment resulted, in our view, from the selectivity of interventions based on the findings of the physical examination and rapid response of the multidisciplinary team in meeting the functional demands characterized by rapid clinical response.

Several studies indicate muscle weakness and fatigue symptoms among long COVID patients.[3,87] FACIT-Fatigue scores were already within the normal range at the baseline evaluation of our patients. Still, our program improved the FACIT-Fatigue scores, however without statistical significance.

Long COVID patients have many risk factors for developing sarcopenia, such as ICU hospitalization,[88] systemic inflammatory processes,[89] metabolic stresses, and chances of insulin resistance in the acute phase.[90] Only one patient was diagnosed with sarcopenia using a Dual Energy X-Ray Absorptiometry (DEXA). Muscle strength evaluation by the MRC sum score could not identify any muscle involvement by the assessments of the handgrip strength, quadriceps ultrasonography, and electrically induced muscle activation.

Like examining muscle strength in high-level athletes, MRC is not the best tool to assess muscle strength in long COVID. Isokinetic assessments also identified evidence of muscle weakness requiring rehabilitation. However, isokinetic training could not capture improvements after our successful rehabilitation treatment.

Despite previous reports of ultrasonography as a surrogate marker of appendicular lean mass,[91] our data demonstrated morphological changes not suggestive of the classic picture of sarcopenia in the elderly.[92] We cannot confirm, however, that the findings resulted from COVID-19 alone, due to the absence of a DEXA study prior to the SARS-COV2 infection.

We consider that the rapid improvement of symptoms was possible due to the reversal of reflex inhibition of multifactorial origin (neuromuscular blocking drugs in intubation, immobilism and sarcopenia, neuropathy, myopathy, pain, and central inhibition). Electrostimulation and pain treatment seemed to be fundamental in this reversal. After overcoming reflex inhibition, there is the possibility of continuing muscle recovery and progression of motor function and joint protection with an exercise program of greater demand. Without this final rehabilitation phase, the patient will still be exposed to painful conditions. Upon starting the rehabilitation program, included patients had a low fatigue threshold.

Regarding the emotional and cognitive aspects, it should be highlighted that even after 14 months of the COVID-19 infection, patients still presented with global cognitive impairment and signs of anxiety and stress, which do not seem to improve spontaneously without specific intervention.

Although the patients' perception and our clinical observation of cognitive and emotional improvements, statistical analyses showed that the psychological interventions did not improve the scores of cognition, depression, and stress. However, it is noteworthy that there was an improvement in anxiety.

Some factors may have contributed to this improvement, such as the psychological intervention process. It was observed that patients had an excellent engagement in the treatment, with good attendance, motivation, and interest in the orientations provided.

This fact probably facilitated the evolution process of patients. The more informed a person is about their physical and mental health condition, cognitive, emotional, and behavioral functioning, and how their treatment can be conducted, the more they will be ready to actively participate in the process.[93]

Patients may also feel validated and hopeful when they know that their problems are cared for by professionals, who may not be as unusual as they imagined and are likely to improve. Psychoeducation can influence treatment success,

increase patient's confidence in the therapeutic approach and broaden their motivation for treatment.[94] In addition, psychoeducation can contribute to the reduction of the symptomatology of the disease, favoring the improvement of quality of life, promoting benefits for the patient and his family,[93] because it makes the patient and the family aware of their responsibility in controlling symptoms, implementing healthy habits and maintaining their health and quality of life.

Besides demonstrating and reporting improvements both in the cognitive and emotional domains at home, patients reported they were more attentive to cognitive issues and possible strategies of emotional control, resignification of life habits, and awareness about the importance of mental health.

In addition, patients with long COVID may also benefit from neuropsychological rehabilitation due to its possible global cognitive deterioration.[2]

We also emphasize the importance of specific psychological and cognitive treatments, combined with a multidisciplinary team approach to be started as soon as possible in long COVID patients. The goal is to take care of mental health, intervening in the prevention and chronification of psychiatric diseases and the possible long-term cognitive decline, improving these patients' functionality and quality of life.

Our psycho-affective intervention did not improve the specific cognition, depression, and stress scores. Due to the relevance of these symptoms in long COVID patients, despite discharge with psycho-affective goals achieved, we suggest the introduction of other interventions that include cognitive, sleep, and mood improvements, in addition to other assessment instruments.

The main nutrition complaint identified in our patients was weight gain after COVID-19. According to BMI, six (50%) patients were classified as overweight and five (41.7%) as obese. Six patients gained weight after hospital discharge. All patients presented with above-average body fat assessed by DEXA and are at risk of diseases associated with obesity. Only one patient scored for sarcopenia.[94]

All patients presented difficulty regarding meal fractionation, non-consumption of whole grains, and low consumption of vegetables, as five individuals complained of constipation T1 or 2 of the Bristol fecal scale.[95] Constipation is directly related to the quality of the diet. A diet rich in vegetables can help reduce inflammation by regularizing intestinal habits.[96]

The change in lifestyle imposed by the COVID-19 pandemic, associated with reduced physical activity, increased sedentary behaviours, sleep changes, anxiety, depression, and negative changes in eating habits such as changes in diet fractioning, absence of regular eating times, or extensive periods of fasting lead to lean mass degradation and consequently increased body fat, in addition to reducing the resting metabolic rate, generating a cycle of body weight increase.[97-99]

Unlike a previous report,[11] we did not find the complaint of continuous loss of taste and smell. However, the quality of food may have been greatly influenced by issues related to the socioeconomic condition of our patients.

Another study proposed that during confinement, a balanced diet with all the necessary nutrients, including healthy fats, balanced levels of sugar and cholesterol, carbohydrates with low glycemic index, and regular physical exercises keep the metabolic balance stable, corroborating with a suggestion published regarding patients after COVID-19.[99] Our patients did not present any oral intake restrictions. Regarding the performance in activities of daily living, according to the patient´s perception, there was an improvement in activities that demanded reaching and manual dexterity, housework activities, bathing, clothing, and personal hygiene. We suspect that the objective improvements in the handgrip strength capacity may have influenced the perceived improvement in the performance skills of the activities of daily living and functional independence, as previously reported.[100,101]

Finally, we observed high variability of disabling symptoms and uniqueness of functional demands related to the physical, cognitive, psychosocial, and nutritional domains observed in long COVID patients. These documented complex rehabilitation needs of fast and unexpected recovery required the team members' integrated, dynamic, prompt, and joint action. The different evaluations allowed us to establish a customized treatment plan with proper interventions. Significant functional improvements were observed even in a patient with an event of stroke onset at the acute phase of SARS-CoV-2 infection.

The functional improvement presented in long COVID patients may mean preventing late complications such as falls and eventual fractures, absence from work, osteoarthritis, dementia, mental disorders, chronic pain, anxiety, depressive and stress conditions.

Strengths of the study

Functional recovery with rehabilitation objectives was achieved in a short period of 58 days.

Study limitations

We acknowledge our limited sample size. That is the reason we opted for more conservative statistical analyses. The Friedman's Test for difference in ranks used in this study is suited for small samples and makes few assumptions on the data, but at the cost of statistical power. This matter, aligned with the already limited power of the sample size, means that we may not have captured differences that had minor effects, which may explain some of the trending results we have found (p-values greater than, but close to 0.05).

Also, due to concerns for statistical power, we opted to analyze only four variables with Friedman's Test and use regression slopes to guide our discussion for the remaining to avoid a significant number of multiple tests. Nevertheless, average slopes are suitable for the purposes being analyzed here and are the basis for conservative tests when comparing two or more groups.[102]

Another study limitation is the absence of a control group and lack of evaluation of the medium and long-term effects. We could not control for selection bias in the sample of this study because several patients equally with rehabilitation demands could not participate in the program. We considered the effect of the intrinsic motivation of these patients on their engagement in the program.

Despite an intense active search, some patients could not attend the program. We provided an application with educational instructions on sleep, nutrition, and physical and emotional aspects. However, there was limited adherence of

the patients. Thus, we could not offer specific interventions for daily sleepiness and insomnia, present in 50% of patients.

CONCLUSION

The optimized and intensive interdisciplinary model of short-term outpatient care developed at the Institute of Physical Medicine and Rehabilitation reduces pain, improves mobility, and anxiety symptoms in long COVID patients with motor, cognitive, psychosocial, and nutritional sequelae.

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