



Retrospective Observational Study

#### INTEGRATED THERMAL CARE AND BIO-PHYSICO-METRIC APPROACH **FOR** THE TREATMENT OF LONG-COVID **PATIENTS**

G. Barassi<sup>1,2\*</sup>, L. Prosperi<sup>2</sup>, R. Pellegrino<sup>3</sup>, A. Di Iorio<sup>4</sup>, V. Guglielmi<sup>2</sup>, A. Younes<sup>2</sup>, C. Marinucci<sup>2</sup>, M.P. Della Rovere<sup>2</sup> and M. Panunzio<sup>5</sup>

<sup>1</sup>Castelnuovo della Daunia Thermal Medicine Center, Castelnuovo della Daunia, Italy;

<sup>2</sup>Center for Physiotherapy, Rehabilitation and Re-Education (Ce.Fi.R.R.) venue "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy;

<sup>3</sup>Department of Scientific Research, Campus Ludes, Off-Campus Semmelweis University, Lugano, Switzerland;

<sup>4</sup>Antalgic Mini-Invasive and Rehab-Outpatients Unit, Department of Innovative Technologies in Medicine & Dentistry,

"G. D'Annunzio" University of Chieti-Pescara, Chieti, Italy;

Correspondence to: Giovanni Barassi, PhD, MSc, PT, DO

Center for Physiotherapy, Rehabilitation and Re-Education (CeFiRR)

University of Chieti-Pescara, "G. d'Annunzio"

Chieti, 66013, Italy

e-mail: coordftgb@unich.it

# **ABSTRACT**

COVID-19 has involved many aspects of society and, in particular, for most of those who were affected by it, the disease determined the development of prolonged pulmonary, musculoskeletal, and neurological symptoms, generating the so-called Long COVID-19 Syndrome. The aim of this study is to evaluate the effects of an Integrated Rehabilitation Care protocol, applied according to principles of assessment and treatment derived from a Bio-Physico-Metric approach, in post-COVID patients. Data from a group of 30 patients affected by Long COVID-19 Syndrome were collected right before the beginning and immediately after the end of an 8-week thermal rehabilitation protocol, performed 5 times a week for a total of 40 sessions of treatment. The Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT), the Medical Research Council Dyspnea Score (MRC-DS), and the software-assessed head-pelvis alignment angle were considered as assessment methods of respiratory, musculoskeletal, and neurological symptoms. Data observation showed a significant improvement in both CAT (p=0.001) and MRC-DS (p=0.001) scores after applying the Integrated Rehabilitation Care protocol. Therefore, the Integrated Thermal Care rehabilitation protocol seems to be a promising strategy to reduce symptoms of Long COVID-19 Syndrome and improve patients' quality of life healing from SARS-CoV-2 infection.

**KEYWORDS**: COVID-19, long haul COVID-19, rehabilitation, physical therapy, thermal care, balneotherapy, mineral waters

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<sup>&</sup>lt;sup>5</sup>Responsible Research Hospital, Campobasso, Italy

#### INTRODUCTION

Coronavirus disease 2019 (COVID-19) can be considered a multi-system disorder, manifesting commonly with respiratory, cardiovascular, hematologic, neurological, and neuropsychiatric symptoms, alone or in combination. Several descriptions of long-term COVID-19 have been documented (1), as well as its multifaceted nature that could involve multiple organ systems and multiple body functions such as breathing, taste and olfactory perceptions, pain perception, physical resistance and strength, etc. (2,3). Many patients affected by COVID-19, with different levels of severity and duration, could develop a so-called Long COVID-19 Syndrome (4-6). In fact, despite improvements in radiologic and lung function tests, Arnold et al. found that the symptoms of COVID-19 may persist and could even evolve into other severe pathologies despite the patient having completely recovered from the viral infection underlying the pathology (7). Although the definition of Long COVID-19 Syndrome is currently still debated and evolving, it is practical and acceptable to define it as the persistence of symptoms or development of sequelae beyond 3 or 4 weeks from the onset of acute symptoms of COVID-19, as replication-competent SARS-CoV-2 has not been isolated after 3 weeks (8). The literature suggests that Long COVID-19 Syndrome could be related to a persistent state of fatigue of the autonomic nervous system (9), involving the prolonged alteration of neurophysiological pathways (10,11). This chronic fatigue at a nervous level, which usually manifests itself already during the infection, would seem to favor the establishment and perpetuation of neurophysiological changes; these modifications are capable of heavily influencing the state of health of the patient, also impacting his neuro-psychological and musculoskeletal wellbeing through sensory, humoral, performance and postural alterations.

Considering the spreading of Long COVID-19 Syndrome and the deleterious effects that this can cause on the health of patients, particularly in the case of frail people already suffering from severe musculoskeletal and neurological pathologies, it is essential for medical and rehabilitation sciences to find treatment strategies for the Syndrome. These therapeutic strategies should be equally widespread in various geographical areas, easily applicable, accessible to large portions of the population, and cheap.

In this context, all over the world, there has been an attempt to investigate new therapeutic approaches based also, among others, on traditional and complementary medicines, such as herbal medicine, Yoga, and Tai Chi, up to the point of considering approaches more complex and specific to the field of global wellbeing and rehabilitation falling within the field of thermal medicine (12).

Thermal medicine is a naturalistic branch of medicine with a wide diffusion worldwide; it is often applied in the treatment of localized and systemic pathologies in curative, preventive, and rehabilitative fields (13) through the use of applications of natural techniques and substances that exploit thermal waters rich in minerals, hot mud, steam jets, assisted ventilation, massages, and swimming pool baths.

According to our previous experiences, a rehabilitation system defined as "Integrated Thermal Care", based on the combination of several treatment techniques typical of thermal medicine, seems to be a promising therapeutic approach in the treatment of many acute and chronic musculoskeletal and neurological pathologies, particularly if combined with the principles of what we define as "Bio-Physico-Metric" approach (14,15). This operative approach is aimed at concretely identifying the most dysfunctional areas of the body of the patient, at a somatic level, to intervene quickly, effectively, and minimally invasively on the neurophysiological and mechano-postural symptoms through mechanisms involving the balancing of the activity of visceral, somatic and nervous components of the human body.

Therefore, given the ability of thermal medicine and the "Bio-Physico-Metric" approach to improve the state of health of subjects affected by a multitude of pathological states, the aim of the present study is to monitor the effects of the "Integrated Thermal Care" approach on pulmonary, musculoskeletal and neuro-physiological signs and symptoms in subjects affected by Long COVID-19 syndrome.

### MATERIALS AND METHODS

This is a retrospective observational study aimed at analyzing the correlation between applying the "Integrated Thermal Care" approach and modifying the symptoms related to Long COVID-19 Syndrome in patients undergoing a thermal rehabilitation protocol. The rehabilitation protocol to which the patients were subjected is safe; it is accessible to all patients who do not highlight specific contraindications to the initial clinical evaluation necessary for all patients who access the facility where the study is carried out; furthermore, the protocol does not constitute an experimental practice, as it is the same therapeutic protocol used for all patients who do not present the aforementioned contraindications.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained at enrolment from participants who were willing and able; alternatively, informed consent was obtained from caregivers. Because of all these considerations and the lack of incontrovertible national legislation regarding the need to submit retrospective and/or non-pharmacological observational studies to an ethics committee, the normal ethics committee clearance was not required (16).

From June to December 2021, in the Thermal Medical Center of Castelnuovo della Daunia (Foggia, Italy), operating within the National Health Service, a total of 30 post-COVID patients were identified among those about to start a therapeutic thermal rehabilitation protocol to regain a state of wellbeing in the presence of a generalized malaise following a previous SARS-CoV-2 infection.

The main inclusion criteria were:

symptoms associated with Long COVID-19 Syndrome as defined by the current literature on the subject (8), in particular in terms of perceived respiratory dysfunctions, neurophysiological dysfunctions (such as fatigue or sleep disorders), musculoskeletal pain and concurrent spinal postural alteration influencing the state of well-being of the patients. The symptoms that have arisen and can be associated with COVID-19 had to be present in the patient, in whole or in part, for more than 4 weeks after their onset post-infection, even if the infection is undetectable by molecular and antigenic swabs.

## The exclusion criteria were:

- critical cognitive impairments (severely limited sensory and communication skills) or heavily compromised immune functions;
- general contraindications to balneotherapy and physical therapies, such as severe cardiovascular problems, infections, neoplasms and tumors, epilepsy, electronic or metallic-electroconductive implants, pregnancy;
- inability to read and understand own native language;
- concomitant use of other medical treatments during the observation period of the present study.

All patients underwent a specific evaluation of neuro-sensory and motor-postural symptoms resulting from Long COVID-19 Syndrome. The data collection and the procedures applied were part of the standard clinical routine of the facility where the study was carried out for patients showing symptoms of Long COVID-19 Syndrome. In order to obtain data that were easily understandable and interpretable, as well as of rapid collection, the patients observed for the present study were evaluated through:

- CAT [Chronic Obstructive Pulmonary Disease (COPD) Assessment Test]: used to evaluate the health status of patients with COPD and other respiratory diseases. Indeed, it contains items focused on respiratory symptoms and non-respiratory symptoms such as sleeping disturbance or limitations in activities at home. In particular, the rating scale is made up of 8 items that investigate various aspects related to the respiratory capacity of the patient, such as cough, mucus, chest tightness, physical resistance to walking, physical resistance to domestic activities, perceived safety in leaving the home environment, noise of the sleep and perceived energy level. Each item assesses the severity of the symptomatology with a score from 0 (no symptoms) to 5 (extremely present and disabling symptom) (17,18). Although the scale was created to evaluate chronic obstructive pulmonary disease, it has been demonstrated that this score can be a valid evaluation and predictive system in the context of COVID-19 and the post-infectious symptoms of the same pathology (19).
- MRC-DS (Medical Research Council Dyspnea Scale): a simple and valid method of categorizing patients with COPD and other respiratory diseases in terms of the influence of the respiratory deficit on their physical capacity. The scale measures the level of dyspnea perceived by the patient in a classification system divided into 5 levels of onset of breathing difficulties depending on the intensity of the activity performed (grade 0 = dyspnea after intense physical activity, grade 1 = dyspnea after walking at fast pace or uphill, grade 2 = dyspnea after walking at a slow pace on level ground, grade 3 = dyspnea after just 100 meters of walking, grade 4 = dyspnea when dressing/undressing). This scale has been successfully applied to evaluate dyspnea in many respiratory diseases, and a new application for COVID-19 monitoring has been recently found (20).
- Sa.B.B. (Safe Bead Balance): it is a postural markers-free assessment tool based on the use of a Microsft Kinect® camera that, when paired with an exclusive software, possesses the ability to reconstruct a three-dimensional avatar known as Skeletal View, composed by 20 anatomical landmarks. The software works at a frequency of 30 frames per second, and each single analysis has a total duration of no more than 5 seconds, with an average capture of 150 frames in a single assessment. The avatar obtained through the combination of all the frames captured is formed by two projections, a frontal one and a sagittal one, which contain and highlight different postural setting parameters both of a single body district and of multiple districts in more

or less direct relationship with each other, such as the spine, the shoulders, the hips and various other bodyparts (21).

For this study, the evaluation parameter considered in the assessment made through the Sa.B.B. software was the head-pelvis alignment, understood as the angle that is formed between the line perpendicular to the center of the pelvis (understood as the center of the bisiliac line) and the line that connects this same point to the ideal center of the skull of the patient, with values that can take on negative numbering (sloping to the right) or positive (sloping to the left). This angle is the most intuitive parameter for evaluating the general postural alignment of the patient in relation to his spine, allowing us to investigate how he positions the skull and, more generally, the upper part of the body compared to the lower one. Basically, through this parameter, we can guess to what extent the spine of the patient is aligned or in a state of compensation for musculoskeletal and/or neurosensory alterations.

The subjects were evaluated at times T0 (admission and first medical examination in the facility) and T1 (8 weeks after the beginning of the protocol). All patients underwent the rehabilitation protocol five times a week for a total of 40 sessions of treatment. All patients observed for this study completed the investigated protocol entirely and without side effects.

The rehabilitation protocol, as defined by the "Integrated Thermal Care" approach, was performed for each daily session according to the following operative scheme:

- 1. drinking a total of 4 glasses, 200 ml each, daily of exogenous mineral water (alkaline-earthy-bicarbonate-sulfate), which promotes the general well-being of the organism, showing anti-inflammatory effects at the gastric, intestinal, and urological levels (22, 23);
- 2. steam inhalations with direct hot humid jets that are carried out through individual devices from which the mineral water comes out from a nozzle in the form of a homogeneous mist at a pressure of 1.5 atmospheres and at a temperature of 37°-38° (24, 25) lasting about 20 minutes. This phase was coupled with a manual pressure stimulation of Key myofascial Trigger Points (KTrPs) located in muscles present in the main body areas involved in breathing (neck, thorax, upper back, lower back, and abdomen). The manual pressure stimulation was performed for about 30 to 60 seconds on each KTrP previously instrumentally identified as abnormally resistant to the passage of a current generated by an impedance meter neuromodulation device (ENF Studio Physio, Fast Therapies S.r.l., Carpenedolo, Italy). The assessment of KTrPs was made by the physiotherapist right before the beginning of the inhalation treatment, according to the principles of the Bio-Physico-Metric approach, aimed at re-establishing a general state of well-being through manual stimulation of so-called KTrPs (26);
- 3. tympanic insufflations (Polizer), used to reduce inflammation in the upper airways (performed according to specialist medical indication) (27);
- 4. pulmonary mechanical ventilation, practiced after inhalation and insufflation therapies with mineral water. The treatment was applied with an automatic frequency of no more than 14 breaths per minute (according to specialist medical indication) (28);
- 5. mud therapy (with thermal water and "Bentonite" volcanic clay) was applied on body parts where KTrPs previously identified in phase 2 were located on the region of the neck, thorax, upper back, lower back, and abdomen (29);
- 6. assisted hydrokinesitherapy in thermal water, associated with the manual treatment performed by the physiotherapist on KTrPs previously identified in phase 2 (30);
- 7. auxiergic vascular path performed in thermal water through underwater ozone-enriched hydromassage jets.

Data were analyzed to assess departure from linearity, using the Skewness and Kurtosis test for linearity (SKTEST procedure) and accordingly for continuous variables (CAT and Sa.B.B.); since no deviation was found, the Paired T-Test was applied to assess between times differences. For categorical variables (MRC-DS), a chi-square test for trend was applied. A statistically significant level was set for *p*-value <0.05; data analysis was performed using STATA (Statacorp LLC, College Station, Texas, USA).

### **RESULTS**

The demographic characterization of the sample is detailed in Table I. It is important to underline that, in addition to the symptoms of Long COVID-19 Syndrome subjectively reported by all the patients considered, some of them, at the time of admission, had CAT ( $\geq$ 10) or MRC-DS ( $\geq$ 2) scores considered symptomatic for COVID-19 respiratory dysfunction according to the standards currently most widespread in the literature (31).

**Table I**. Demographics characteristics of participants.

Characteristic	Total	Males	Females
Number of patients (%)	30 (100)	15 (50)	15 (50)
Mean age ± SD	$58.8 \pm 12.8$	$58.1 \pm 15.2$	$59.5 \pm 10.3$
Ethnicity			
Caucasian Mediterranean (%)	30 (100)	15 (50)	15 (50)
Other (%)	0 (0)	0 (0)	0 (0)
Initial CAT Score ≥10 (%)	23 (77)	12 (40)	11 (37)
Initial MRC-DS Score ≥2 (%)	12 (40)	6 (20)	6 (20)
Initial CAT Score ≥10 + MRC-DS Score ≥2 (%)	11 (37)	6 (20)	5 (17)

All patients successfully completed the total sessions required for the rehabilitation protocol, and no adverse events were detected at any stage of the treatment process. CAT score showed a statistically significant reduction (T0=16.76 $\pm$ 8.48; T1= 8.73 $\pm$ 5.22, *p*-value <0.001), indicating a halving of the severity of respiratory and fatigue symptoms perceived by patients in relation to the presence of Long COVID-19 Syndrome. At the same time, the value of Sa.B.B. head-pelvis alignment angle highlighted a reduction in the value (T0=2.38 $\pm$ 3.20; T1= 1.95 $\pm$ 3.06, *p*-value not statistically significant) which, although not statistically significant, could indicate that the treatment had a modest effect on the postural setting of the treated patients, particularly at the spine level, despite the very high variability of the initial and final reference values, highlighted by the large standard deviation values detected during the analysis (Table II).

**Table II**. Paired T-Test results for continuous variables.

Variable	T0	T1	<i>p</i> -value
CAT Score	16.76±8.48	$8.73\pm5.22$	< 0.001
Sa.B.B. head-pelvis alignment angle	$2.38\pm3.20$	$1.95\pm3.06$	n.s.

Finally, the categorical variable MRC-DS highlighted a statistically significant (for trend p-value <0.001) reduction in the severity of dyspnea related to the presence of Long COVID-19 Syndrome in patients (Fig. 1); in fact 20/30 (66%) subjects improved their symptomatology, whereas 9/30 (30%) were stable and only one subjects worsened, with a general reduction in the mean value detected before and after treatments (T0=1.53±0.97; T1=0.80±0.66). The reduction of the two scores evaluated significantly improves the well-being of subjects observed for the study.

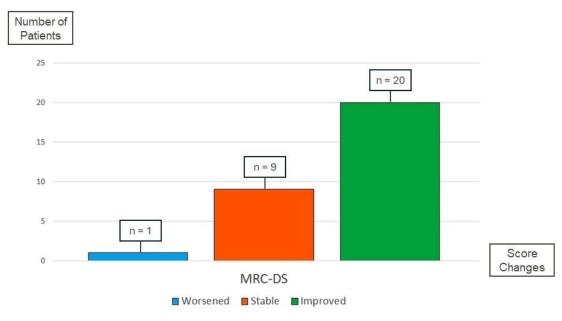


Fig. 1. Changes in MRC-DS Scores after the rehabilitation protocol (chi-square test for trend analysis).

#### DISCUSSION

The main results of our study underly that after 8 weeks of rehabilitation through the principles of "Integrated Thermal Care" combined with the "Bio-Physico-Metric" approach, patients showed a significant improvement in CAT and MRC-DS scores but only a slight non-significant improvement in the Sa.B.B. head-pelvis alignment angle.

Long-term management of COVID-19 symptoms requires multiple, multidimensional approaches (32) and can benefit from evidence-based complementary techniques, such as thermal medicine (12). Thermal medicine has, in fact, a centuries-old tradition as a therapeutic approach and is widely spread in different parts of the world where thermal realities constitute an important element of mass therapy. It is relatively simple, economical, and usable by a large portion of the local population, presenting some differences in the physical-chemical characteristics of the specific thermal environments (12).

The World Health Organization itself, by virtue of the therapeutic potential of traditional and complementary medicines, hopes for the development of a scientific investigation regarding the application of these alternative medicines to identify strategies for the containment of widely spread pathologies, especially in a context of globalization which could promote the increasingly frequent emergence of pandemics such as COVID-19 (33). It is important to ensure that the medical environment is prepared as much as possible to face global health emergencies, exploiting every existing therapeutic approach that is sufficiently effective and scientifically investigated, even in the case of traditional, alternative, and complementary medicines. It is no coincidence, in this regard, that the World Health Organization has committed itself to promoting, over the last decade, a program of investigation and development of traditional and complementary medicines carried out from 2014 to 2023 and extended until 2025 while waiting to evaluate the effects and possible future developments (33).

Based on these considerations, in this study, we tried to evaluate a methodologically more scientific and structured approach in the context of rehabilitation for Long COVID-19 Syndrome. In this approach, patients received treatments typical of thermal therapy combined with manual (somatic) stimulation of KTrPs identified through the Bio-Physico-Metric pathway, aiming to restore the best possible somato-visceral reflex activity and vice versa.

This approach is based on observing objective measurement parameters to identify dysfunctional areas defined as KTrPs. These specific points are overstimulated areas within a contracted band found in the myofibrils of a muscle belly (34), characterized by a chronic circumscribed myofibrillar shortening. KTrPs contribute to establishing and maintaining musculoskeletal dysfunctions and neurological symptoms directly (from the local inflammatory process and mechanical alteration) and indirectly (through reflex neurophysiological pathways and systemic inflammation). KTrPs are characterized by palpatory tenderness, referred tension, motor dysfunction, and autonomic manifestations (34). In addition to manifesting themselves locally, these symptoms often take on the characteristics of distant irradiation, following the dermatomal path of the area originally affected and leading to the genesis of Satellite Trigger Points at a distance from the KTrP. These irradiative and expansive phenomena of KTrPs increase their dysfunctional intrusiveness, favoring the perpetuation and chronicity of musculoskeletal and neurophysiological symptoms (34). The stimulation of KTrPs, through manual treatment and/or through instrumental stimulation (electrical, thermal, or mechanical), tends to reduce pain and functional limitations, as well as neuro-sensory symptoms determined locally and/or systemically by KTrPs (27).

Indeed, to reduce symptoms from Long COVID-19 Syndrome, subjects were treated with typical thermal medicine techniques in combination with soft tissue manipulative therapy and mud application on the identified KTrPs through the use of an impedance meter neuromodulation device.

The improvement of respiratory symptoms and fatigue observed through the CAT and the MRC-DS scores was obtained through the association of hydroponic and inhalation treatments and a multimodal stimulation (manual, with hot mud and assisted hydrokinetic therapy) of the KTrPs in the muscle of the areas bodily involved in breathing, as already observed by us in other pathological contexts (13). In this regard, the current literature on the topic suggests that the symptoms of Long COVID-19 Syndrome can persist in the human body for very long intervals, on average ranging from 3 months to over 6 months (8,20). Considering that the patients analyzed in this study had respiratory and psychophysical symptoms of COVID-19 for at least 4 weeks at the time of admission and that the duration of the treatment protocol was 8 weeks, it seems unlikely that the detected improvements of the CAT and MRC-DS scores were purely the result of the time that has passed since the first assessment was carried out. This appears in agreement with what was highlighted by a large prospective study on the subject, which showed that in patients suffering from Long COVID-19 Syndrome, CAT and MRC-DS scores would appear to improve to a limited or non-existent extent in the absence of adequate therapeutic intervention (20).

Equally interesting are the considerations that can be made regarding the influence of the treatment protocol on the postural setting of the treated subjects. By observing the variation between T0 and T1 of the head-pelvis alignment

angle value detected using the Sa.B.B. system, it seems that the Integrated Thermal Care treatment coupled with the Bio-Physico-Metric Approach was able to induce positive variations in the postural setting of patients, with an explicit although not significant tendency towards postural realignment at the level of the spine. This phenomenon was detected despite a very high variability and lack of homogeneity in the starting postural malalignment values of the 30 patients observed in this study, which allows us to assume the possibility of obtaining a clearer and more marked positive effect in populations that are more homogeneous regarding the degree of postural dysfunction. In fact, the literature highlights that postural dysfunctions would require to be considered in a very specific way, from an evaluative and therapeutic point of view, both with regard to the demographic characteristics of the sample analyzed and the body systems and subsystems involved (35). For example, it is known that Long COVID-19 Syndrome is often associated with the presence of the so-called Postural Orthostatic Tachycardia Syndrome, in the presence of which it is possible to witness the appearance of autonomic symptoms in relation to the posture assumed by infected subjects (36, 37).

In a recent review on Long-Covid (38), many of these things were elucidated, also covering the fields of microthrombi (39), mainly IL-1 induced (40), and the rare case of anaphylaxis among the vaccinated population (41). The proposed project paves the way to devote more attention to the blood white cells, as well-known messenger monocytes (42-43) and macrophages, through charging from the ACE receptor and P2X7 receptor (44).

Increased fatigue severity is associated with stronger signs of monocyte activation in long COVID patients, potentially pointing toward monocyte-endothelial interaction. These abnormalities were present against a background of immune abnormalities common to the entire group of long COVID patients.

The correlations with Long-Covid deserve new insights. The Integrated Thermal Care and Bio-Physico-Metric Approach for treating Long-Covid is a proposal that can help Long-Covid patients overcome correlated difficulties better.

Considering the reciprocal influence existing between the nervous system and the musculoskeletal system, the results of this study, although characterized by a mixed magnitude and significance, seem to confirm that an approach based on both metabolic and musculoskeletal stimulations might be able to positively influence complex pathologies like Long COVID-19 Syndrome, especially if the stimuli are provided according to specific and organized operative principles, such as those of the Bio-Physico-Metric Approach (27).

Despite the relatively small sample size, this protocol seems to cover a broad range of positive effects on patient's health, even for mostly neurologically induced manifestations such as breathing difficulties in the absence of clear pulmonary anomalies and symptoms such as fatigue and sleep disturbances.

This study, however, presents some limitations. Firstly, the characteristics of the sample appear to be small in relation to the general diffusion of Long COVID-19 Syndrome and rather heterogeneous by virtue of the observational nature of the study, which prevented the characteristics of the sample (age, sex, BMI, and comorbidities) from being meticulously standardized. Secondly, there is a lack of an extended follow-up to observe the effectiveness of the protocol in the medium-long term, which would be desirable to better monitor the evolution of Long COVID-19 Syndrome characterized by a duration of specific symptoms that tends to be rather long. Thirdly, there is an evident lack of a control group that could allow us to evaluate the magnitude of the protocol implemented in speeding up recovery from Long COVID-19 Syndrome. To bypass these limitations, further studies with a larger and more homogeneous sample, subjected to a follow-up long after the intervention and to the comparison with a control group, would be necessary to define a relevant protocol.

However, we must also consider some important strengths of our study and, more generally, the observational research in the context of widespread pathologies such as COVID-19 and its syndromic derivations. First of all, observational studies such as the one proposed allow us to identify and monitor in a real situation the therapeutic potential of some treatment approaches that would otherwise find little interest in research, bypassed by the predominant pharmacological and surgical approaches (45, 46). This allows us to identify, at least on a preliminary basis, the complementary and alternative approaches in which it is worth investing in research, thus reducing the costs and timing of identifying new therapeutic avenues, especially in rapidly spreading pathologies such as Long COVID-19 Syndrome (45, 46).

Furthermore, it has been observed several times in the literature that, contrary to what is commonly believed in the scientific field, there is a quite close concordance between the results of well-designed observational studies and controlled and randomized studies on the same topic, obviously provided that the observations are accompanied by a correct and honest analysis of potential biases (46). Finally, it should be highlighted that the results of observational studies in the therapeutic field are often difficult to dispute when the magnitude of the results obtained is so important as to be incontrovertible (47). Net of this, we believe that our study, without having any presumption of having identified a new therapeutic gold standard in the treatment of Long COVID-19 Syndrome, could provide the right ideas to investigate the therapeutic potential of an approach that finds its strengths in its reduced invasiveness and high tolerability by patients. We may also outline the high level of adherence to the protocol highlighted in the patients under observation.

The timing and the relationship with the health professionals increased curiosity and motivation to undergo the protocol, providing better adherence to the therapies, which translated into positive therapeutic results in accordance with the principles of the Biopsychosocial model of health (48). This positive finding of our study is also particularly relevant since it has been observed that psychosocial symptoms like depression, fear, and kinesiophobia, which are also typically associated with Long COVID-19 Syndrome, may have a negative impact on the quality of life and pain perception of these patients (49). Given the general positivity of the results obtained, the rehabilitation approach proposed in the present study could represent a new vision of cooperating between thermal care and rehabilitation with a view to defining a new, structured and scientifically validated alternative therapeutic approach to Long COVID-19 Syndrome.

### **CONCLUSIONS**

Long COVID-19 Syndrome affects multiple organ systems, and its management requires a comprehensive approach. This may include the association between thermalism and somatic therapy of the dysfunctional reflex areas, which often represent the expression of internal organic and neurological dysfunctions leading to the genesis of symptoms such as pain, sensory alterations, fatigue, and postural alterations. This approach can improve health outcomes, at least in the short term, while reducing unnecessary hospital admissions, thus preventing the depletion of healthcare resources that have already been significantly strained worldwide during the COVID-19 pandemic.

Since the Long COVID-19 Syndrome can be particularly disabling and also occur in fragile subjects affected by neuromuscular pathologies that reduce their movement capabilities and tolerance to active work, a minimally invasive treatment approach such as the one observed in this study could represent a valid complementary or alternative therapeutic solution compared to classic approaches to date proposed for the syndrome (such as athletic reconditioning through physical exercise). Larger and more structured studies are needed regarding the approach we observed; confirming the positive results we obtained in a purely observational setting would allow us to expand the therapeutic arsenal to address the long-term consequences of a pandemic-wide pathology such as COVID-19. In fact, based on observations of the data obtained, the proposed "Integrated Thermal Care" protocol could be an innovative approach that improves the health status of COVID-19 patients, helping them recover even from the long-term effects of the pathology.

Despite the limitations, the high adherence to the protocol and the significant improvements observed in this study provide a basis for further research. Larger, randomized, controlled trials with longer follow-up periods are needed to confirm these preliminary results and demonstrate the long-term efficacy and safety of the protocol.

In conclusion, while this study provides promising evidence for the use of Integrated Thermal Care and the Bio-Physico-Metric approach in the treatment of Long COVID-19 Syndrome, further research is needed to address the limitations of the current study and to validate the effectiveness of this rehabilitation strategy fully.

# Conflict of interest and funding

The authors declare that they have no conflicts of interest regarding this study. No external funding has been received to carry out the research.

# **REFERENCES**

- 1. Callard F, Perego E. How and why patients made Long Covid. *Social Science & Medicine*. 2021; 268:113426. 10.1016/j.socscimed.2020.113426
- 2. McMahon DE., Gallman AE, Hruza GJ, et al. COVID in the skin: a registry analysis of COVID-19 dermatological duration. *The Lancet Infectious Diseases*. 2021; 21(3):313-314. 10.1016/S1473-3099(20)30986-5
- 3. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5–6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax*. 2021; 76(4):405-407. 10.1136/thoraxjnl-2020-216377
- 4. Lu Y, Li X, Geng D, et al. Cerebral micro-structural changes in COVID-19 patients—an MRI-based 3-month follow-up study. *EClinical Medicine*. 2020; 25. 10.1016/j.eclinm.2020.100484
- 5. Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open.* 2021; 11(3):048391. 10.1136/bmjopen-2020-048391
- Townsend L, Dowds J, O'Brien K, et al. Persistent poor health after COVID-19 is not associated with respiratory complications or initial disease severity. *Annals of the American Thoracic Society*. 2021; 18(6):997-1003. 10.1513/AnnalsATS.202009-1175OC
- 7. Arnold DT, Hamilton FW, Milne A, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*. 2021; 76(4):399-401. 10.1136/thoraxjnl-2020-216086
- 8. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nature Medicine*. 2021; 27(4):601-615. 10.1038/s41591-021-01283-z

 Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, Lim PB. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clinical Medicine*. 2021; 21(1):63. 10.7861/clinmed.2020-0896

- 10. D'Ardes D, Carrarini C, Russo M, et al. Low molecular weight heparin in COVID-19 patients prevents delirium and shortens hospitalization. *Neurological Sciences*. 2021; 42:1527-1530. 10.1007/s10072-020-04887-4
- 11. Lombardi G, Paganelli R, Abate M, et al. Leukocyte-derived ratios are associated with late-life any type dementia: a cross-sectional analysis of the Mugello study. *Geroscience*. 2021; 43(6):2785-2793. 10.1007/s11357-021-00474-3
- Bailly M, Evrard B, Coudeyre E, et al. Health management of patients with COVID-19: is there a room for hydrotherapeutic approaches? *International Journal of Biometeorology*. 2022; 66(5):1031-1038. 10.1007/s00484-022-02246-w
- 13. Scanu A, Tognolo L, Maccarone MC, Masiero S. Immunological Events, Emerging Pharmaceutical Treatments and Therapeutic Potential of Balneo therapy on Osteoarthritis. *Front Pharmacology*. 2021; 12:681871. 10.3389/fphar.2021.681871
- 14. Barassi G, Panunzio M, Di Iulio A, et al. Integrated Thermal Rehabilitation Care: An Intervention Study. *Healthcare*. 2023; 11(17):2384. 10.3390/healthcare11172384
- 15. Barassi G, Di Simone E, Supplizi M, et al. Bio-Physic-Metric approach: integrated postural assessment in musculoskeletal dysfunctions. *Journal of Biological Regulators and Homeostatic Agents*. 2022; 36(1):129-135. 10.23812/21469L
- 16. Winter EM, Maughan RJ. Requirements for ethics approvals. *J Sports Sci.* 2009; 27(10):985. 10.1080/02640410903178344
- 17. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J.* 2009; 34:648–654. 10.1183/09031936.00102509
- 18. Houben-Wilke S, Janssen DJA, Franssen FME, Vanfleteren LEGW, Wouters EFM, Spruit MA. Contribution of individual COPD assessment test (CAT) items to CAT total score and effects of pulmonary rehabilitation on CAT scores. Health and Quality of Life Outcomes. 2018; 16:1-8. 10.1186/s12955-018-1034-4
- 19. Freund O, Breslavsky A, Givoli-Vilensky R, et al. Assessment of a close respiratory follow-up schedule at 3 and 6 months after acute COVID-19 and its related investigations. *Respir Med.* 2023; 217:107367. 10.1016/j.rmed.2023.107367
- 20. Cheng SL Lin CH, Wang CC, et al. Comparison between COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores for evaluation of clinical symptoms, comorbidities and medical resources utilization in COPD patients. *Journal of the Formosan Medical Association*. 2019; 118(1):429-435. 10.1016/j.jfma.2018.06.018
- 21. Barassi G, Bellomo RG, Carmignano SM, Di Felice PA, Giannuzzo G, Leggieri M, D'Ettole S, Saggini R. Flexible software for the elimination of the markers used in the analysis of human posture through kinect® sensor. *Archives of Physio-therapy & Global Researches*. 2016; 20(1).
- 22. Matsumoto S. Evaluation of the Role of Balneo therapy in Rehabilitation Medicine. *J Nippon Med Sch.* 2018; 85(4):196-203
- 23. Aversano A, Rossi FW, Cammarota F, De Paulis A, Izzo P, De Rosa M. Nitrodi thermal water downregulates protein S-nitrosylation in RKO cells. *Int J Mol Med.* 2020; 46(4):1359-1366. 10.3892/ijmm.2020.4676
- 24. Dessanges JF. A history of nebulization. J Aerosol Med. 2001; 14(1):65-71. 10.1089/08942680152007918
- 25. Sanders M. Inhalation therapy: an historical review. Prim Care Respir J. 2007; 16(2):71-81. 10.3132/pcrj.2007.00017.
- 26. Barassi G, Pellegrino R, Di Matteo C, et al. Bio-Physico-Metric Approach: Assessment and Treatment of Key Myofascial Trigger Points through an Adaptive Neuromodulation Device. *Journal of Biological Regulators and Homeostatic Agents*. 2023; 37(1):25-29. 10.23812/j.biol.regul.homeost.agents.20233701.3
- 27. Califano L, Salafia F, Mazzone S, D'Ambrosio G, Malafronte L, Vassallo A. A comparative randomized study on the efficacy of a systemic steroid therapy vs. a thermal therapy in otitis media with effusion in children. *Minerva Pediatr*. 2016; 68(4):241-249.
- 28. Maccari JG, Teixeira C, Gazzana MB, Savi A, Dexheimer-Neto FL, Knorst MM. Inhalation therapy in mechanical ventilation. *J Bras Pneumol*. 2015; 41(5):467-472. 10.1590/S1806-37132015000000035.
- 29. Tateo F, Ravaglioli A, Andreoli C, Bonina F, Coiro V, Degetto S, Giaretta A. The in-vitro percutaneous migration of chemical elements from a thermal mud for healing use. *Appl. Clay Sci.* 2009; 44:83–94. 10.1016/j.clay.2009.02.004
- 30. Becker BE. Aquatic therapy: scientific foundations and clinical rehabilitation applications. *Pm&r*. 2009; 1(9):859-872. 10.1016/j.pmrj.2009.05.017.
- 31. Johnsen S, Sattler SM, Miskowiak KW, et al. Descriptive analysis of long COVID sequelae identified in a multidisciplinary clinic serving hospitalised and non-hospitalised patients. *ERJ Open Res.* 2021; 7(3):00205-2021. 10.1183/23120541.00205-2021
- 32. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med.* 2021; 27(4):601-661. 10.1038/s41591-021-01283-z
- 33. World Health Organization (WHO). Global strategy on traditional medicine (EB152/18). Fifteenth meeting of World Health Executive Board, World Health Organization, Geneva, 6th February; 2023. Available: https://apps.who.int/gb/ebwha/pdf\_files/EB152/B152(18)-en.pdf.

34. Donnelly JM, Fernández-de-las-Peñas C, Finnegan M, Freeman JL. *Travell, Simons & Simons' Myofascial Pain and Dysfunction: the Trigger Point Manual.* 3rd ed. Wolters Kluwer: Alphen aan den Rijn; 2018

- 35. Saggini R, Anastasi GP, Battilomo S, et al. Consensus paper on postural dysfunction: recommendations for prevention, diagnosis and therapy. *J Biol Regul Homeost Agents*. 2021; 35(2):441-456. 10.23812/20-743-A
- 36. Raj SR, Arnold AC, Barboi A, et al. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. *Clin Auton Res.* 2021; 31(3):365-368. 10.1007/s10286-021-00798-2
- Rigo S, Urechie V, Diedrich A, Okamoto LE, Biaggioni I, Shibao CA. Impaired parasympathetic function in long-COVID postural orthostatic tachycardia syndrome - a case-control study. *Bioelectron Med.* 2023; 9(1):19. 10.1186/s42234-023-00121-6
- 38. Grohmann G, Booy R. An update on Long COVID. Microbiology Australia. 2024; 45(1): 18-21. 10.1071/MA24007
- 39. Knight R, Walker V, Ip S, et al. Association of COVID-19 with major arterial and venous thrombotic diseases: a population-wide cohort study of 48 million adults in England and Wales. *Circulation*. 2022; 146(12):892-906. 10.1161/CIRCULATIONAHA.122.060785
- 40. Conti P, Caraffa A, Gallenga CE, et al. IL-1 induces throboxane-A2 (TxA2) in COVID-19 causing inflammation and micro-thrombi: inhibitory effect of the IL-1 receptor antagonist (IL-1Ra). *J Biol Regul Homeost Agents*. 2020 34(5):1623-1627. 10.23812/20-34-4EDIT-65
- 41. Bellomo RG, Gallenga CE, Caraffa A, Tetè G, Ronconi G, Conti P. Anaphylaxis is a rare reaction in COVID-19 vaccination. *J Biol Regul Homeost Agents*. 2021; 35(3):839-842. 10.23812/BELLOMO\_EDIT\_3\_21
- 42. Berentschot JC, Drexhage HA, Aynekulu Mersha DG, et al. Immunological profiling in long COVID: overall low grade inflammation and T-lymphocyte senescence and increased monocyte activation correlating with increasing fatigue severity. *Frontiers in Immunology*. 2023; 14:1254899. 10.3389/fimmu.2023.1254899
- 43. Scott NA, Pearmain L, Knight SB, et al. Monocyte migration profiles define disease severity in acute COVID-19 and unique features of long COVID. *European Respiratory Journal*. 2023; 61(5). 10.1183/13993003.02226-2022
- 44. Gallenga CE, Maritati M, Mura M, Di Virgilio F, Conti P, Contini C. Macrophage Activation in Follicular Conjunctivitis during the COVID-19 Pandemic. *Microorganisms*. 2023; 11(9):2198. 10.3390/microorganisms11092198
- 45. Barnish MS, Turner S. The value of pragmatic and observational studies in health care and public health. *Pragmatic and observational research*. 2017; 8:49-55. 10.2147/POR.S137701
- 46. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *New England Journal of Medicine*. 2000; 342(25):1878-1886. 10.1056/NEJM200006223422506
- 47. Black N. Why we need observational studies to evaluate the effectiveness of health care. *Bmj*. 1996; 312(7040):1215-1218. 10.1136/bmj.312.7040.1215
- 48. Thurner C, Stengel A. Long-COVID syndrome: physical—mental interplay in the spotlight. *Inflammopharmacology*. 2023; 31(2):559-564. 10.1007/s10787-023-01174-4.
- 49. Brindisino F, Garzonio F, Di Giacomo G, Pellegrino R, Olds M, Ristori D. Depression, fear of re-injury and kinesiophobia resulted in worse pain, quality of life, function and level of return to sport in patients with shoulder instability: a systematic review. J Sports Med Phys Fitness. 2023; 63(4): 598-607. 10.23736/S0022-4707.22.14319-7