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Balneotherapy for the treatment of post-COVID syndrome: a randomized controlled trial

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Abstract

Background Post-Acute COVID Syndrome (PACS) is a complex disorder that currently lacks effective evidenced-based therapies to manage it. This randomized controlled trial aims to evaluate the effects of balneotherapy (BT) on PACS symptomatology.

Methods Ninety-eight adults with PACS visited at Hospital del Mar Research Institute, Barcelona (Spain) were included to the study. Participants in the intervention group ($n=51$) were allocated to 12 sessions of BT and aquatic exercises delivered in one month while the control group ($n=47$) did not. The primary outcome was to evaluate the absolute change in questionnaire scores between baseline and two follow-up points: immediately after balneotherapy (or one-month post-baseline for the control group) and 2 months post-baseline. The following scales/questionnaires were employed: Post-COVID-19 functional status scale, mMRC dyspnea Scale, SF-36, Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), Memory failures in everyday life following severe head injury, and Visual Analogic Scale (VAS).

Results Forty-seven patients in the BT group and 43 in the control group completed the study. The majority of participants were middle-aged women (> 84%; mean age 48 years), and the most prevalent symptoms were fatigue, musculoskeletal pain, and neurocognitive impairment (> 88%). Noteworthy, the vast majority did not undergo a severe primary infection (ICU admissions < 3%). After BT, significant improvement was detected in the BT group vs. the control group in various SF-36 domains, PSQI total score (Beta-coefficient [95%CI] 2.641 [1.15;4.12]; p -value = 0.003), HAD's anxiety subscale (Beta-coefficient [95%CI] 1.72 [0.40;3.03;*p*-value = 0.023), and VAS (Beta-coefficient [95%CI] 1.625 [0.32;2.96]; *p*-value = 0.026). Among these, SF-36's energy/fatigue and pain subscales exhibited the most prominent changes with a Beta-coefficient [95%CI] of -17.45 [-24.23;-10.66] and −21.634 [-30.48;-12.78], respectively (*p*-value < 0.0001). No severe adverse effects were reported during BT although seventeen patients reported mild and transient worsening of preexisting symptoms, particularly fatigue/post-exertional malaise mainly in the first sessions of BT.

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Conclusion Balneotherapy comprise an effective therapeutic modality that can alleviate several symptoms that characterize PACS, particularly musculoskeletal pain and fatigue. However, the sustainability of these effects over time remains uncertain, as evidenced by the loss of some between-group differences at the one-month follow-up.

Trial registration ClinicalTrials.gov NCT05765591 (13/03/2023).

Keywords Balneotherapy, Post-COVID-19 syndrome, Patient reported outcome measures

Background

Since the outbreak of the COVID-19 pandemic, an immense number of scientific publications and lines of research have been generated around the acute phase of the SARS-CoV-2 infection. Less attention has been drawn on the long-term complications that a number of patients develop subsequently, i.e., the Post-Acute COVID Syndrome (PACS) [1]. PACS, commonly termed as long COVID, has been defined by the World Health Organisation (WHO) as persistence or development of new symptoms 3 months after the initial SARS-CoV-2 infection. Symptoms last for at least 2 months and cannot be explained by an alternative diagnosis [2]. The clinical spectrum is extremely broad: patients experience mild to incapacitating symptoms that indicate affectation of multiple organs and systems including neurological, cardiovascular, heart, digestive, dermatological and musculoskeletal systems among others. The prevalence of symptoms varies according to series, but some of the most frequently reported complaints include fatigue, musculoskeletal pain, shortness of breath, cognitive dysfunction, sleep disturbances, and mood disorders [3]. PACS's underlying pathophysiology is still unclear, although it is speculated that it results from the sum effects of direct viral damage, chronic inflammation, and altered immune response [4]. Given that the estimated prevalence of PACS, according to the WHO, is 10–20% of people recovering from an acute SARS-CoV-2 infection [2], the burden that this disorder poses on affected individuals, healthcare providers and society is increasingly worrying.

At present, there are no specific pharmacological interventions that have demonstrated effectiveness in treating PACS as a whole entity given the large array of manifestations that characterize this disorder, and its unclear pathophysiology [3, 5]. Pharmacological treatment is typically individualized on the basis of each patient's particular manifestations, although evidence-based studies are currently lacking on this respect. More efforts have been made in studying the response to different rehabilitative modalities with promising results [6, 7]. In this regard, a small study with patients with PACS with secondary impaired upright posture, showed beneficial effects of aquatic exercise techniques on motor function, microcirculation, and anxiety/depression subscales [8]. Indeed, aquatic exercises, particularly if performed in natural thermal mineral waters, i.e., balneotherapy (BT) [9], is a common and popular adjuvant treatment for numerous chronic conditions, particularly but not limited to rheumatic disorders [10]. The mechanisms by which BT appear to exert its benefits are not fully clear, but is to thought derive from the thermal and hydrostatic pressure stimulation, buoyancy, and the unique mineral salt composition of each natural spring [11–13].

In an effort to investigate new therapeutic options for patients with PACS, we conducted a randomized trial, in which the acceptability and effects of BT in the thermal waters of Caldes de Montbui (Barcelona, Spain), were explored through patient reported outcome measures in a cohort of affected patients.

Methods

Participants

Patients were recruited in the multidisciplinary Post-COVID unit of the Hospital del Mar or in a primary care center in Barcelona (Spain). In addition, Caldes de Montbui's City Council also advertised the project for patient recruitment on its public website. Individuals willing to participate underwent an initial visit in which clinical data was reviewed for eligibility. Inclusion criteria were individuals ≥ 18 years old with a Post-Acute COVID Syndrome (PACS) diagnosis, according to WHO criteria [2], provided by a physician. PACS diagnosis was based on a history of confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.

Common symptoms include fatigue, shortness of breath, cognitive dysfunction/brain fog, cough, musculoskeletal pain, headache, post-exertional malaise, sleep disorders,

tachycardia/palpitations, among others, and generally have an impact on everyday functioning.

Exclusion criteria included patients with pre-existing disorders to the acute SARS-CoV-2 infection that displayed an important clinical overlap with PACS i.e., fibromyalgia (FM), chronic fatigue syndrome, chronic pain, and generalized anxiety disorder and/or depression that required pharmacological treatment. Patients with chronic debilitating conditions that required active treatment were also excluded i.e. cancer, chronic viral infections, systemic autoimmune diseases, epilepsy,

uncontrolled endocrine disorders, etc. Patients with fear of water, incontinence, severe venous insufficiency, physical disabilities that hindered performance of BT, and those who reported a tendency for symptomatic low blood pressure were also excluded. Blood tests performed within 4 months or less before the initial visit were mandatory for preselection and were reviewed: patients with anaemia, CKD stage 4 or less, chronic liver insufficiency, thyroid function abnormalities, and in general, any significant blood test abnormality that could be associated with PACS-related symptomatology, were excluded. Recruited participants were randomly assigned to the intervention or control group through a lottery method (1:1). Allocation concealment was done using the Sequentially-Numbered, Opaque, Sealed Envelopes (SNOSE) method. After opening an envelope, the participant and the physician administering the interventions became aware of the intervention assigned to that participant, but the outcome analyst remained blinded. Patients were asked to not vary their usual care or initiate any other kind of therapy during the duration of the study.

Clinical data collection at baseline

At the time of the initial visit several clinical parameters were registered including: age, sex, Body Mass Index (BMI), date of SARS-CoV-2 infection, admission into the Intensive Care Unit (yes/no), Visual Analogue Scale (VAS), SARS-CoV-2 vaccination status, and a large array of PACS-related symptoms (yes/no) that were classified according to the system/organ affected (Supplemental Table 1).

Study design

This study was designed as a prospective open-labelled randomized controlled trial (RCT: NCT05765591; date 13/03/2023). Data was collected at 3 time points: (1) initial visit (baseline), (2) at the end of BT or one month after baseline in control group, and (3) one month after BT finalization or two months after baseline in control group.

Balneotherapy (BT) intervention

The BT intervention consisted of 3 weekly sessions on alternate days in groups of 8 during 4 weeks, i.e., 12 sessions in total. BT was accompanied of exercises in the water pool. The weekly planning was structured as following:

1st day: Pool, inhalation, shower, and aquatic exercise.

2nd day: Pool, inhalation, shower.

3rd day: Pool, inhalation, shower, and aquatic exercise.

The exercise program was designed by qualified specialists from the Caldes de Montbui spa.

BT [9] was performed in the thermal water pool, at 35 °C during 2 h. At the start of the session, patients were instructed to inhale thermal water vapor for 10 min, alternating between nose and mouth. Subsequently they underwent a circular shower during 10 min with a very fine jet that ran from the ankles to the neck to activate circulation. The temperature of the water and the power of the jet was set by the patient. Next, they started the exercise program which lasted 15 min and was structured as follows:

1st : Ankle joints workout, knee flexions, and abductors workout.
2nd : Waist and arm rotation.
3rd : Arm raise exercises: arms were raised and lowered from legs to mid-waist. Subsequently, the same exercise was repeated but raising concomitantly knees and, if possible, clapping hands above the head.
4th : Hand exercises: patients were instructed to open and close their hands first, and then, repeated the same exercise but alternating hiding or exposing their thumbs.
5th : Lateral neck movements.
6th : Cycling and rowing movements while holding onto the pool's wall.
7th : Walking 2 laps around the pool.
During the last 15–20 min patients were allowed to relax in the whirlpool.

In regards to water composition, the natural thermal springs of Caldes de Montbui have a meteoric origin and, and even though their temperature is high, they are classified as telluric [14, 15]. They are also considered highly mineralized as they have a dry residue at 110 °C of 1235 mg/L (threshold value > 1000 mg/l). Caldes de Montbui springs are mainly composed of sodium chloride waters containing 74.5% mEq chloride anions and 90.3% mEq sodium cations. They are also classified as very soft as the CaCO3 concentration is 56.6 mg/L [14].

Control group

Patients from the control group were instructed to not participate in any BT-related activity and/or new therapeutic exercise program during the duration of the study and to continue with usual pharmacological care and regular daily activities.

Primary outcomes

To evaluate the effects of BT we employed an array of validated self-reported questionnaires that covered an important part of PACS symptomatology. The primary outcome of the study was to evaluate differences in

questionnaire scores from baseline between both groups. The following scales and questionnaires were employed:

1) *Post-COVID*-19 functional status scale (PCFS): an ordinal scale that assesses functional limitations associated to PACS. It ranges from grades 0 (best) to 4 (worst) [16].
2) mMRC (Modified Medical Research Council) Dyspnoea Scale: stratifies the severity of dyspnea in day-to-day activities. It ranges from grades 0 (best) to 4 (worst) [17].
3) *Short Form-36* Health Survey (*SF-36*): instrument for the objective measure of the quality of life cover eight domains of health. Each subdomain ranges from 0 (worst) to 100 (best) [18].
4) Pittsburgh Sleep Quality Index (PSQI): assesses sleep quality and sleep disturbances. It ranges from 0 (best) to 21 (worst). A score ≥ 5 indicates poor sleep [19, 20].
5) Hospital Anxiety and Depression Scale (HADS): designed to identify states of depression and anxiety in a medical outpatient clinic setting. Each subscale ranges from 0 (best) to 21 (worst). The cut-off scores for anxiety and depression are 7 and 8, respectively [21].
6) Memory failures in everyday life following severe head injury (MFE-30): questionnaire that evaluates the incidence of memory failures in everyday life. It ranges from 0 (best) to 120 (worst). A score ≥ 36 indicates significative amnesic impairment [22, 23].
7) Visual Analogic Scale (VAS): represents a unidimensional measure of pain intensity. It ranges from 0 (best) to 10 worst [24].

The percentage of individuals within each group that showed any improvement in the questionnaires' scores at timepoints 2 and 3 compared to baseline were also calculated and compared between groups.

Safety assessment was performed in all the patients who had received at least one session of BT and the adverse events were monitored during BT.

Statistical methods

The sample size was calculated from an internal study [25] of our group in patients experiencing some type of osteoarticular pain in which VAS pain scale was measured to them at entry, before the thermal treatment, and one month later. Before treatment the mean (SD) of the pain scale was 5.7 (2.4), and 1 month later 3.5 (2.3). A sample size calculation was performed with these data applying the GRANMO (Hospital del Mar Research institute) program. Accepting an alpha risk of 0.05 and a beta risk of less than 0.2 in a bilateral contrast, 40 subjects in the first group and 40 in the second group are needed to detect a difference in VAS equal to or greater than 2 units. The common standard deviation is assumed to be 3. A loss to follow-up rate of 10% has been estimated.

Data analysis was performed in a blinded manner.

Descriptive statistics were used for demographic and clinical characteristics related to PACS. Comparisons between groups for quantitative variables were performed by t-test and chi-square tests were used for qualitative variables. Questionnaire scores were analysed at baseline and, for the follow up, using the intra-individual absolute change between baseline and post-BT or one month after baseline (control group), and between baseline and one month after completing BT or two months after baseline (control group). One-way ANOVA was used for comparisons between groups. Univariate General Linear Model (GLM) was used for group comparisons adjusted by age and BMI. Benjamini-Hochberg Adjusted *P*value (FDR) [26] was applied for multiple testing correction. Finally, the change between time points was also categorized according to whether score improvement was observed (yes/no). Chi-square test was used to perform the corresponding comparisons between groups and to obtain de Relative Risk (RR). Statistical analysis was done using SPSS Statistics version 22.0. *P*values lower than 0.05 were considered significant. Figures were prepared with Prism 8 (GraphPad Software, La Jolla, CA, USA).

Results

Patients

A total of 129 participants contacted via e-mail and 98 were finally included in the intention-to-treat study according to eligibility criteria. Fifty-one patients were randomly allocated to the balneotherapy group and 47 to the control group (Fig. 1). Four participants in the balneotherapy group withdrew from the study: 2 of them due to BT-associated adverse effects, and the other 2, due to injuries that were not related to the intervention. Four patients from the control group did not respond to any of the follow-up questionnaires.

Finally, 47 patients from the intervention group and 43 from the control group completed the study (Fig. 1) and were included in the outcome analyses.

Patient characteristics and symptomatology at baseline are listed in Tables 1 and 2, respectively. Fatigue, musculoskeletal pain, and neurocognitive impairment were the most prevalent symptoms in our cohort (prevalence > 88%). The majority of participants were middle-aged women (> 84% women; average age 48 years old), and the vast majority did not undergo a severe primary infection (ICU admissions < 3%) corroborating that PACS can develop across all degrees of disease severity [4]. Our cohort stands out for its very long-lasting

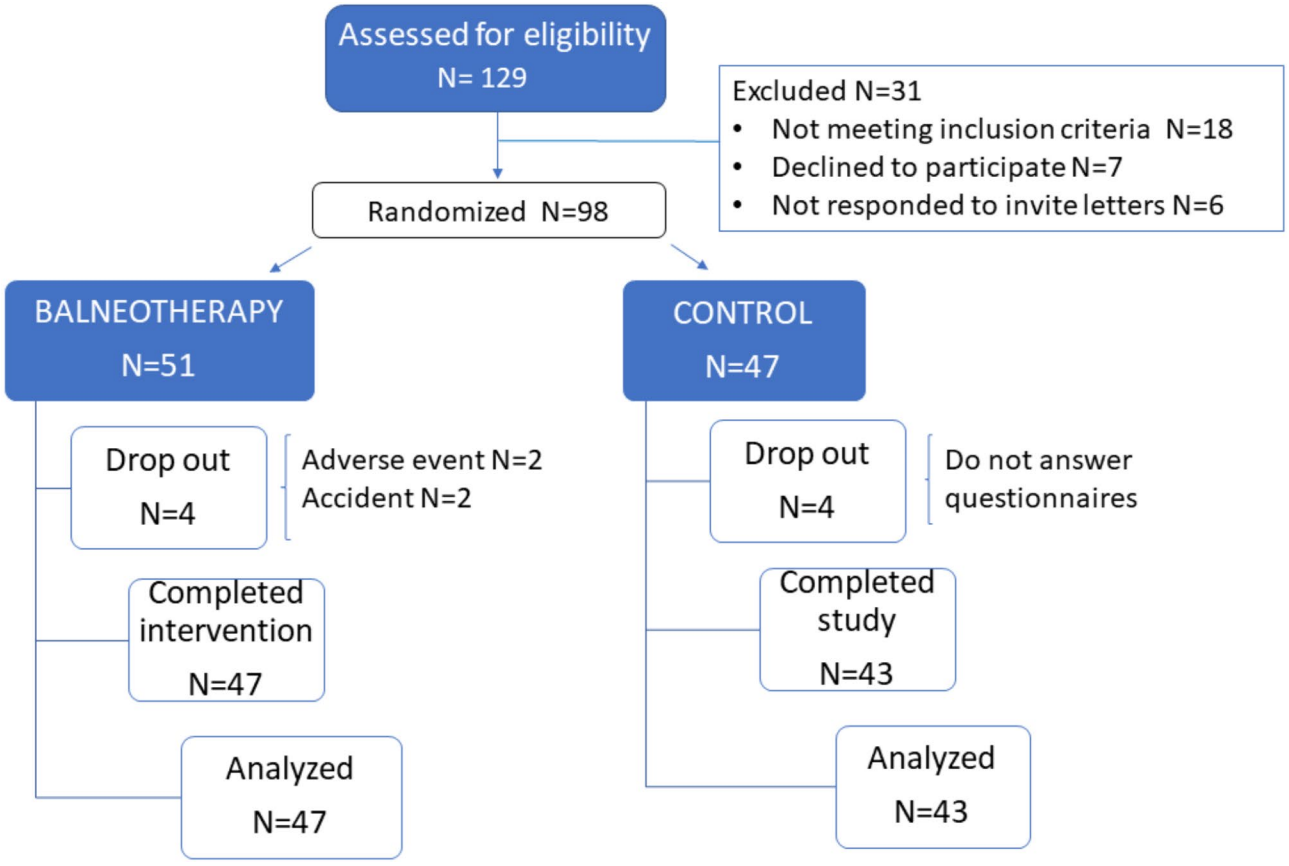

Fig. 1 Flowchart showing the number of patients recruited and their respective study group allocation. Drop out reasons: In the Balneotherapy group, 2 individuals withdrew due to fatigue and dizziness during the first sessions of balneotherapy, and the other 2, due to accidents not associated with the intervention. In the Control group, 4 individuals did not answer the follow-up questionnaires

Table 1 Patient characteristics at baseline

	Participants, No./total, No. (%)	
	Balneotherapy *N* = 51	**Control *N* = 47**
Sex (% female)	45/51 (88.2)	39/47 (83.0)
Age, years (mean ± SD)	47.84 ± 9.93	48.95 ± 8.43
BMI kg/m^2 (mean ± SD)	25.8 ± 5.4	25.54 ± 4.52
ICU admission (%)	2/51 (3.9)	1/47 (2.1)
SARS-Cov-2 vaccination status	complete	complete
Year of COVID-19 primoinfection (%)		
2020	36/51 (70.6)	34/47 (72.3)
2021	14/51 (27.5)	12/47 (25.5)
2022	1/51 (2)	1/47 (2.1)

Abbreviations: BMI: body mass index; ICU: Intensive Care Unit. Complete vaccination was considered when patients had received at least 2 doses of vaccine

symptomatology, with > 97% presenting persisting symptoms for more than 1 year and > 67% for nearly 2 years (Table 1).

No significant baseline differences were found in demographic characteristics, features, and illness condition between the groups.

Individual absolute change in questionnaire scores during follow-up

Baseline values of questionnaire scores are listed in Table 3. No significant differences were found between study groups.

One month after baseline, significant improvement was detected in most scales in the balneotherapy group compared to control group (Figs. 2 and 3). Differences between groups remained significant after

Table 2 Post-acute COVID syndrome symptomatology at baseline

	Participants, No./total, No. (%)	
	Balneotherapy *N* = 51	**Control *N* = 47**
Fatigue	50/51 (98.1)	43/47 (91.5)
Chest pain/tightness	38/51 (74.5)	27/47 (57.4)
Fever/permanent dysthermic sensation	18/51 (35.3)	10/47 (21.3)
Cardiovascular	37/51 (72.5)	28/47 (59.6)
Respiratory	46/51 (90.2)	35/47 (74.5)
Neurological/ Neurocognitive	50/51 (98)	47/47 (100)
Digestive	38/51 (74.5)	32/47 (68.1)
Musculoskeletal pain	46/51 (90.2)	40/47 (85.1)
Dermatological	44/51 (86.3)	40/47 (85.1)
Mood disorder	37/51 (72.5)	38/47 (80.9)

Table 3 Baseline values of questionnaires scores. Means were compared between balneotherapy and control groups

	Balneotherapy	**Control group**	**p-value**
	***N*=51**	***N*=47**	
	Mean (SD)	**Mean (SD)**	
PCFS	2.55 (0.67)	2.51 (0.66)	0.732
mMRC Dyspnoea Scale	1.75 (0.73)	1.44 (0.84)	0.060
SF-36			
•Physical functioning	44.9 (17.16)	51.44 (21.83)	0.102
•Role limitations due to physical health	21.04 (21.46)	28.93 (23.02)	0.087
•Role limitations due to emotional problems	62.23 (28.5)	56.1 (23.2)	0.258
•Energy/fatigue	15.9 (14.66)	24.33 (19.93)	0,051
•Emotional well-being	58.17 (19.57)	50.66 (20.85)	0.071
•Social functioning	37.26 (22.88)	35.55 (21.64)	0.709
•Pain	23.33 (19.74)	30.55 (23.91)	0,109
•General health	34.13 (14.8)	33.66 (15.27)	0.879
PSQI	11.86 (4.21)	11.13 (4,17)	0.394
HADS			
•Anxiety	8.27 (4.08)	9.82 (5.28)	0.106
•Depression	9.42 (4.4)	9.95 (4.12)	0.542
MFE-30	53.65 (25.64)	48.28 (28.58)	0.332
VAS	5.67 (2.17)	5.05 (2.72)	0.221

Results are displayed as means ± SD. P-values were calculated by One-way ANOVA. Abbreviations: PCFS (Post-COVID-19 functional status scale); mMRC (Modified Medical Research Council) Dyspnea Scale; SF-36 (Short Form-36 Health Survey) questionnaire; PSQI (Pittsburgh Sleep Quality Index); HADS (Hospital Anxiety and Depression Scale); MFE-30 (Memory failures in everyday life following severe head injury); VAS (Visual Analogic Scale)

adjusting by age and BMI (Table 4). These included VAS (p-value = 0.026) and most of the SF-36 subscales: role limitations due to physical health (p-value = 0.026), role limitation due to emotional problems (p-value = 0.023), energy/fatigue (p-value < 0.0001), emotional well-being (p-value = 0.003), social functioning (p-value < 0.0001), and pain (p-value < 0.0001) (Fig. 2). Among these, SF-36's energy/fatigue and pain subscales exhibited the most prominent reductions with a Beta-coefficient [95%CI] of -17.45 [-24.23;-10.66] and − 21.634 [-30.48;-12.78], respectively.

PSQI total score (i.e., sleep quality) (p-value = 0.003) and HAD's anxiety subscale (p-value = 0.023) also improved significantly with BT (Fig. 3).

In contrast no differences were observed in the PCFS, mMRC Dyspnoea Scale, MFE-30, HAD's depression subscale, and in SF-36's General Health and Physical functioning domains.

One month after BT, some differences between groups were lost including sleep quality and all emotional and mental health-related parameters (Figs. 2 and 3). Persistent improvement at follow-up remained in the intervention group in the SF-36's role limitations due to physical health (p-value = 0.011), and social functioning scales (p-value = 0.005), but again, most significantly, in pain (Beta-coefficient [95%CI] -15.99 [-25.36;-6.63]; p-value = 0.005) and energy/fatigue scales (Beta-coefficient [95%CI] -16.52 [-24.23;-10.66]; p-value = 0.00015) (Fig. 2; Table 4). Means of absolute change of questionnaire scores and Benjamini-Hochberg adjusted p-values between baseline and follow up time points are shown in supplemental Table 2.

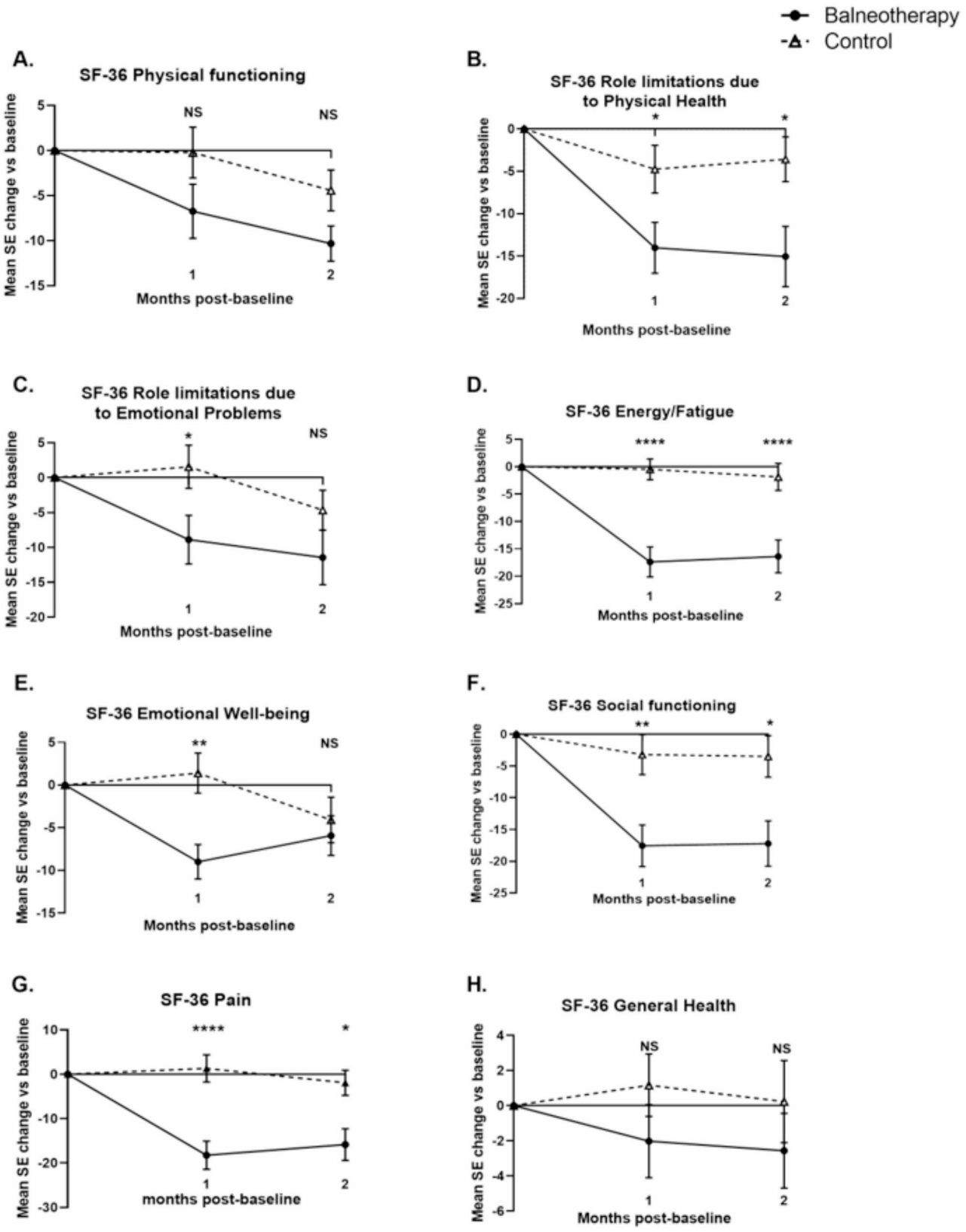

Fig. 2 Differences between study groups in mean absolute changes in SF-36 questionnaire scores at follow-up timepoints vs. baseline. Data are expressed as mean (SE). *P*-values were obtained using One-way ANOVA and FDR-adjusted. A decrease in follow-up scores vs. baseline indicates improvement in the scales. Abbreviations: NS: not significant. Significance: *$p < 0.05$; **$p < 0.01$; ***$p < 0.0001$; ****$p < 0.00001$

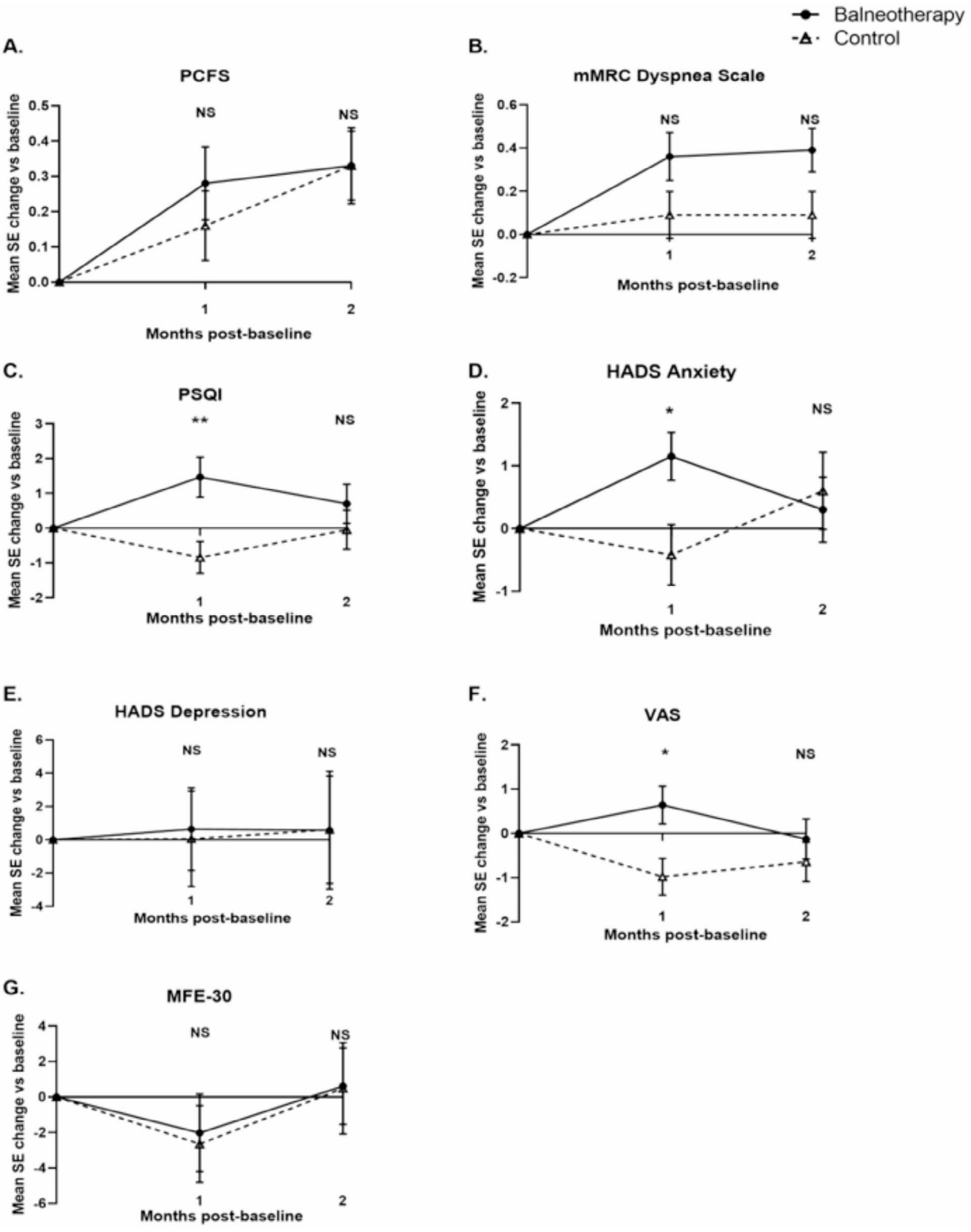

Fig. 3 Differences between study groups in mean absolute changes in PCFS, mMRC, PSQI, HADS, VAS, and MFE-3 questionnaire scores at follow-up time-points vs. baseline. Data are expressed as mean (SE). *P*-values were obtained using One-way ANOVA and FDR-adjusted. An increase in the follow-up scores vs. baseline indicates improvement in the scales. Abbreviations: PCFS: *Post-COVID*-19 functional status scale, mMRC: Modified Medical Research Council, PSQI: Pittsburgh Sleep Quality Index, HADS: Hospital Anxiety and Depression Scale, VAS: visual analogic scale, MFE-30: Memory failures in everyday life following severe head injury. NS: not significant. Significance: *$p < 0.05$; **$p < 0.01$

Table 4 Univariate General Linear Model analysis of absolute change between time points of questionnaire scores adjusted by BMI and age

Questionnaires/scales	post-balneotherapy vs. control group		one month after balneotherapy vs. control group	
	Beta-coefficient [95%CI]	FDR p-value	Beta-coefficient [95%CI]	FDR p-value
PCFS	0.131 [-0.165;0.427]	0.448	0.16 [-0.281;0.313]	0.916
mMRC Dyspnoea Scale	0.267 [-0.54;0.588]	0.153	0.35 [0.05;0.65]	0.069
SF-36 Scale				
Physical functioning	-5.873 [-12.24;0.501]	0.718	-6.187 [-12.24;-0.12]	0.115
Role limitations due to physical health	-10.634 [-19.04;-2.22]	**0.026**	-13.582 [-22.50;-4.66]	**0.011**
Role limitations due to emotional problems	-12.663 [-22.27;-3.04]	**0.023**	-9.258 [-18.84;0.33]	0.124
Energy/fatigue	-17.45 [-24.23;-10.66]	**<0.0001**	-16.52 [-24.32;-8.71]	**0.00015**
Emotional well-being	-11.356 [-17.75;-4.96]	**0.003**	-3.598 [-10.77;3.578]	0.535
Social functioning	-16.513 [-25.55;-7.47]	**<0.0001**	-15.956 [-25.43;-6.47]	**0.005**
Pain	-21.634 [-30.48;-12.78]	**<0.0001**	-15.998 [-25.36;-6.63]	**0.005**
General health	-2.519 [-8.065;3.028]	0.448	-2.993 [-9599;3.614]	0.555
PSQI	2.641 [1.15;4.12]	**0.003**	1.096 [-0.466;2.657]	0.311
HADS				
Anxiety	1.72 [0.40;3.03]	**0.023**	-0.154 [-1.775;1.468]	0.911
Depression	0.562 [-0.730;1.855]	0.448	0.232 [-1.225;1.688]	0.911
MFE-30	1.168 [-5.235;7.570]	0.718	0.785 [-6.113;7.681]	0.911
VAS	1.625 [0.32;2.96]	**0.026**	0.536 [-0.817;1.888]	0.586

Beta-coefficient [95% confident interval] and Benjamini-Hochberg adjusted (FDR) *p*-values are displayed. Abbreviations: PCFS (Post-COVID-19 functional status scale); mMRC (Modified Medical Research Council) Dyspnea Scale; SF-36 (Short Form-36 Health Survey) questionnaire; PSQI (Pittsburgh Sleep Quality Index); HADS (Hospital Anxiety and Depression Scale); MFE-30 (Memory failures in everyday life following severe head injury); VAS (Visual Analogic Scale)

Table 5 Adverse effects detected during balneotherapy

Symptoms	Participants, No./Total No. (%)		
	YES	YES, only first week	Total (*n*=17)
Dizziness	4/17 (23.5)	6/17 (35.3)	10/17 (58.8)
Dysnea or increased dysneic sensation	2/17 (11.8)	1/17 (5.9)	3/17 (17.7)
Hypotension	3/17 (17.7)	5/17 (29.4)	8/17 (47.1)
Nausea	2/17 (11.8)	0/17 (0)	2/17 (11.8)
Fatigue	10/17 (58.8)	10/17 (58.8)	16/17 (94.1)
Sinusitis	2/17 (11.8)	1/17 (5.9)	3/17 (17.7)
Sore throat	3/17 (17.7)	1/17 (5.9)	4/17 (23.5)
Palpitations	3/17 (17.7)	2/17 (11.8)	5/17 (29.4)
Headache	4/17 (23.5)	4/17 (23.5)	8/17 (47)
Weakness	10/17 (58.8)	10/17 (58.8)	16/17 (94.1)
Myalgia	2/17 (11.8)	9/17 (52.9)	11/17 (64.7)
Arthralgia	3/17 (17.7)	6/17 (35.3)	9/17 (52.9)
Ear pain	2/17 (11.8)	1/17 (5.9)	3/17 (17.7)
Abdominal pain	1/17 (5.9)	1/17 (5.9)	2/17 (11.8)

Improvement assessment

Very similar results were observed when data was compared through qualitative categorization of improvement (Supplemental Fig. 1). Again, SF-36's pain and energy/fatigue domains showed the largest magnitude of improvement with a RR of 2.8 [1.69;4.64] and 2 [1.31;3.05], respectively (p-value < 0.0001). Likewise, some mental health related items, significantly improved in the intervention group just after the BT (RR > 1.8;p-value > 0.001), became similar between groups one month later.

Safety

Seventeen patients within the balneotherapy group reported adverse effects, most of which were accentuations of preexisting symptoms, particularly fatigue/post-exertional malaise (Table 5). Importantly, most these symptoms appeared during the first sessions of BT and subsided thereafter. Two patients withdrew from the study during the first week of the intervention due to excessive fatigue and dizziness. No severe adverse effects were reported. In general, compliance within the intervention group was recorded and was very high (> 98%).

Discussion

Management of patients with post-COVID syndrome requires a tailored and holistic approach due to the wide clinical spectrum that this patient population exhibit, both in terms of variety of symptoms and degree of severity. Unfortunately, data on effective pharmacological interventions are lacking probably owing to the gaps of knowledge concerning its underlying pathophysiology. On the other hand, the role of different rehabilitation disciplines has emerged as promising in managing specific symptoms [27]. In this line, we present an interventional study with the aim to evaluate the role of BT plus aquatic exercises in treating post-COVID symptomatology through validated patient-reported outcomes

measures. Significant improvements in pain, vitality, fatigue, sleep quality and diverse mental health parameters were detected in those patients that underwent one month of BT compared to the control group, with acceptable tolerability and an excellent safety profile. This study contributes to pave the way to search for effective therapeutic options in this often underrecognized patient group population due to the clinical variability and lack of an objective diagnostic approach [28].

Patients in our cohort reported typical manifestations ascribed to the PACS clinical constellation reflecting the multisystemic nature and complexity of the disorder [4]. Fatigue, musculoskeletal pain, and neurocognitive impairment were the most prevalent symptoms in our cohort and the majority of participants were middle-aged women which is in line with the literature [4, 29]. Our cohort stands out for its very long-lasting symptomatology, with >97% presenting persisting symptoms for more than 1 year and >67% for nearly 2 years. Of note, most of the patients had not been able to return to their former professional occupations which is in contrast with other series of patients which were able to return to work within 6 months after the acute SARS-Cov-2 infection in spite of developing persisting symptoms [30]. This suggests that patients infected with the earlier SARS-Cov-2 variants were more prone to develop more severe and/or longer-lasting PACS. This data also indicates that patients in this study were within the most severe end of the spectrum.

Musculoskeletal pain and fatigue, cardinal manifestations within the PACS clinical constellation, were the symptoms that improved to a greater extent in the intervention group after completing 4 weeks of BT. These findings were further corroborated by the VAS analysis at this time point. In addition, SF-36 questionnaires revealed maintenance of the beneficial effects on pain and fatigue/vitality domains at one-month follow-up. These outcomes appear particularly relevant given the overwhelming prevalence of fatigue and musculoskeletal pain in our cohort, its profound impact on patients' quality of life, and frequent lack of response to traditional pain killers (data not shown). While the physiopathology of post-COVID syndrome's is still unknown, obvious clinical overlap concerning musculoskeletal pain, in addition to fatigue and sleep disturbances, has been found with fibromyalgia (FM) [31]. In this regard, a meta-analysis on the effects of BT on patients with FM (5 RCTs, 177 participants) showed moderate evidence for a medium-to-large size decrease in pain scores. Several mechanisms have been proposed to contribute to the analgesic effects of balneotherapy including a rise in beta-endorphins, muscle relaxation, decrease in inflammatory mediators, and an increase in pain threshold due to the effects of warm temperature and hydrostatic pressure on nerve endings [32, 33]. Overall, these findings indicate that BT together with pool based-exercises are a promising therapeutic alternative in treating two of the most prevalent and debilitations manifestations in patients with post-COVID.

Significant improvements were also evidenced in the intervention group in other QoL-related subscales, as per the SF-36 questionnaire assessment. These included social functioning, role limitations due to physical health, emotional well-being and role limitations due to emotional problems. However, except for longer-lasting benefits observed in social functioning and role limitations due to physical health, improvements in the other subscales subsided at one month of follow-up. Preexisting reports in which the effects of BT on QoL in patients with FM, have shown heterogenous findings among the different subscales employed, but in all of them, in agreement with our study, intervention lead to generalized small improvements [34–37].

Anxiety scores evaluated through the HADs questionnaire displayed significant reductions at the end of the intervention. This agrees with the improvements observed in the emotional domains in the SF-36 form. Sleep disturbances, which are interrelated with anxiety, were also very common in our cohort and also displayed transitory improvement after BT. In regards to prior studies, the effects of BT and/or aquatic exercises seem to have inconsistent effects on mood and anxiety [8, 38–41] and sleep quality [42, 43]. Overall, it appears that the effects of BT on mood disorders and sleeplessness in the setting of PACS might be mild and transitory, but not entirely negligible.

Concerning neurocognitive impairment, we only assessed subjective memory complaints through the MFE-30 scale [44], which did not change after BT. We acknowledge that in spite of this tool's validation, self-reported outcomes are not optimal for assessing cognitive dysfunction and perhaps we might have dismissed any significant impact on other spheres of cognition. In addition, to date there has not been any formal research on the effects of BT on cognitive function in any setting, so it is difficult to extract clear conclusions on its ineffectiveness in this area.

In our study, no changes were observed in the PCFS and mMRC scales. Although specific to COVID-19 infection, PCFS has been seldomly employed in studies, most of them being of cross-sectional design. It is possible that the generalist character of this scale is not sensitive to detect subtle improvements in specific areas of functionality.

Several aspects should be considered when interpreting our findings. The unblinded design and short follow-up were perhaps the most important limitations, the latter hindering the assessment of the duration of

the benefits observed with some scales. The fact that we have evaluated the effects of both balneotherapy and aquatic exercises together, precluding the assessment of the efficacy of each intervention by itself. However, it is very common in the literature, and in usual practice, that both interventions are combined as an integrative therapeutic approach to a given condition. Some typical PACS manifestations were not studied at all including peripheral neuropathies, together with cardiovascular, dermatological, and digestive abnormalities. In addition, only self-reported outcomes were employed; this appears to be particularly insufficient in the evaluation of cognitive functions which are better studied through conducted interviews. However, a very important number of clinical features within the PACS are subjective complaints without objective forms of evaluation, and for the majority of them, we disposed of validated and appropriate questionnaires. Also, our cohort was comprised of patients which, given their long-lasting, broad, and incapacitating symptomatology, appeared to be within the most severe end of the clinical spectrum, and thus, limiting the generalization of our findings to all patients with PACS. Nonetheless, the study also has important strengths; this is the first study that investigates the effects of BT in patients with PACS, showing clear effectiveness in diminishing some symptoms. In addition, this study was designed in a prospective, controlled, and randomized manner thereby reducing potential biases. Finally, to date, our study is one of the few prospective interventional studies performed on PACS, importantly contributing to offer evidenced-based therapeutic options for these patients.

Conclusions

Our findings indicate that BT and aquatic exercises comprise a rehabilitative modality that can alleviate several symptoms that characterize PACS, particularly musculoskeletal pain and fatigue. While larger-scaled RCTs are needed to confirm our results, the robustness on some of the outcomes indicate that BT deserves to be considered as part of the multidisciplinary and individualized therapeutic approach that this patient population require.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CKD	Chronic kidney disease
FDR	False discovery rate
FM	Fibromyalgia
HADS	Hospital anxiety and depression scale
ICU	Intensive care unit
MFE-30	Memory failures in everyday life following severe head injury
mMRC	Modified medical research council
PACS	Post-acute COVID syndrome
PCFS	Post-COVID-19 functional status scale
PSQI	Pittsburgh sleep quality index
QoL	Quality of life
SD	Standard deviation
SE	Standard error
SF-36	Short form-36 health survey
SNOSE	Sequentially-numbered, opaque, sealed envelopes
RCT	Randomized controlled trial
RR	Relative risk
VAS	Visual analogic scale
WHO	World health organisation

Supplementary Information

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Supplementary Material 1

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Author contributions

DO, DL, and NGG designed and conceptualized the study. DO and NGG analyzed the data, drafted the report, and prepared the final manuscript. DO, AR, and NGG managed database. XN and RGF revised study critically for relevant clinical content. JVG, MTR, and RGF recruited patients and collected data. All authors reviewed, revised, and edited the draft and the final manuscript. The authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

The study protocol was approved by the ethics committee of Parc de Salut Mar (Exp number 2021/10072/I) and it was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Trial status

The study is completed.

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