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CASE REPORT

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Whole-body hyperthermia as part of a multimodal treatment for patients with post-covid syndrome – a case series

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ABSTRACT

Background: Post-Covid syndrome (PCS) has been an ongoing challenge since the COVID-19 pandemic. Relatively little is known about the effect of whole-body hyperthermia (WBH) in the treatment of PCS.
Methods: We retrospectively analyzed the data of patients with PCS who were treated as inpatients with a multimodal integrative therapy approach including WBH. The primary outcome comprised changes in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) between T0 (at hospital admission) and T2 (four weeks after discharge), secondary outcomes were changes in Fatigue Impact Scale (FIS-D), Multidimensional Dyspnea Profile (MDP) and Covid-Associated Symptoms (CAS) between T0–T1 (at discharge) and T0–T2.
Results: FACIT-F yielded a significant increase ($p < 0.001$) between T0 (19.1 ± 8.4) and T2 (29.9 ± 13.0) (primary outcome), indicating an improved health status. While FIS-D and CAS scores improved significantly between T0 and T2, dyspnea parameters improved only between T0 and T1. 63% of respondents identified WBH as an effective treatment.
Conclusions: Study results provide preliminary evidence for potentially positive effects of WBH in the setting of this study, in which it is embedded in a multimodal therapy approach. The results should be substantiated by future RCTs to identify specific effects of individual therapy components.

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1. Introduction

The COVID-19 pandemic has proven to be among the greatest health and societal challenges of recent decades, with over 700 million documented cases of infection and 7 million deaths [1]. In addition to the potentially severe acute course of the disease, prolonged health restrictions after surviving the acute infection are a major and relevant problem [2]. Depending on duration, health restrictions are referred to as long COVID (4–12 weeks after SARS-CoV-2 infection) or post-COVID syndrome (PCS) (beyond 12 weeks). According to the National Institute for Health and Care Excellence (NICE) and German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Working Group of the Scientific Medical Societies) guidelines, PCS is defined as a sequela of COVID-19 infection characterized by symptoms such as fatigue, dyspnea, loss of smell and taste, and general pain that persist for more than 12 weeks after SARS-CoV-2 infection that cannot be explained by an alternative diagnosis [3,4]. Fatigue is the most common symptom [5], affecting 58% of patients with long-term effects of COVID-19 [6]. In a prospective observational study conducted in Germany, approximately 45% of patients who continued to suffer from moderate to severe fatigue six months after a mild to moderate SARS-CoV-2 infection met the Canadian Consensus Criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [7], an overlap of symptoms reported in various publications [8–10]. The long-term sequelae of COVID-19 also include respiratory symptoms such as dyspnea, exercise-induced breathlessness, breathing pattern disorders or persistent cough, as well as headaches, attentional disorders, mental health issues (e.g., depression, anxiety) and autonomic dysfunction characterized by a dysregulation of heart rate variability (HRV) [6,11,12].

The conventional medical treatment of PCS includes physiotherapy, rehabilitation training, psychological support, and treatment of symptoms such as cough, chest pain and myalgia [4,13–15]. Therapeutic approaches from integrative medicine (IM) and complementary and alternative medicine (CAM) have been incorporated to augment conventional therapies in the respective healthcare systems of several countries, and have been utilized and evaluated during the pandemic for the treatment of COVID-19 and PCS across different settings [16–18]. In 2023, a systematic review summarized the current research on various IM approaches in the treatment of PCS,

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including acupuncture, Tai Chi, Ayurveda, homeopathy, naturopathic medicines, vitamins, and phytotherapy [19].

Whole-body hyperthermia (WBH) is a therapeutic approach using controlled overheating of the body in the fever range (38.5–40.5 °C) over a defined period of time to generate pleiotropic effects on the immune system and to promote the physiological functions of immunocompetent cells, as well as intra- and extracellular regeneration processes [20–22]. WBH is used for various conditions such as fibromyalgia [23,24], depression [25,26] and oncological diseases [27,28], and its potential as a novel approach for neurodegenerative disorders and long COVID is discussed in a recent review [22]. Specialized hospitals that practice CAM have established WBH as part of their holistic therapy setting.

Since the suspected pathomechanisms in PCS, such as a persistent dysregulation of the immune system [4], as well as common PCS symptoms, e.g., fibromyalgia-like pain and depression, overlap with the mode of action and the established range of applications of WBH, the procedure appears to be a reasonable treatment option for PCS. On the other hand, it is unclear how patients who predominantly experience fatigue and exhaustion tolerate WBH, which can be a strenuous procedure. To our knowledge, there is only one published case report on WBH as part of a naturopathic complex therapy for PCS from a specialized hospital (Waldhausklinik Deuringen, Stadtbergen) [29], but no other published studies with a larger sample of patients with PCS treated with WBH.

At the Paracelsus Hospital Unterlengenhardt, an anthroposophic hospital in southwest Germany, a multimodal integrative therapy concept for inpatients with PCS has been established. In addition to conventional medicine, the setting comprises WBH as an essential component, accompanied by approaches from anthroposophic medicine (AM).

Given the paucity of published work on WBH in the context of PCS, a condition of ongoing relevance [10], we conducted a retrospective data analysis (case series) of inpatients with PCS who received WBH as part of their multimodal therapy at the Paracelsus Hospital. In doing this, we wanted to find out how patients with PCS evaluate WBH within the multimodal therapy. We hypothesized that more than 50% of patients would rate WBH positively and that patients' FACIT-F scores would improve.

2. Material and methods

2.1. Study design and sample

The present study was conducted as a single setting retrospective case series based on data collected at the Paracelsus Hospital Unterlengenhardt and was approved by the ethics committee of the Baden-Württemberg Medical Association (approval number: F-2023-106). The study was conducted in accordance with the Declaration of Helsinki and registered in the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS, registration number: DRKS00033018, date of registration: 2023-11-13, retrospective registration).

The study analyzed data from patients admitted to the Paracelsus Hospital Unterlengenhardt for treatment of PCS from February to December 2021. During this period of time, a set of questionnaires was given to all patients to obtain patient feedback on the multimodal therapy concept that had been established for the treatment of PCS and was being monitored for its validity. The present case series is based on these questionnaire data.

Prior to the initiation of treatment, all patients were verbally informed about the multimodal IM therapy concept by the attending physicians. IM approaches were specified and WBH procedure was explained in detail, with patients being advised that the procedure could be perceived as strenuous and informed of possible risks. Depending on the type of WBH with potentially high temperatures, patients undergoing the procedure may be at increased risk for cardiovascular stress and destabilization of metabolic and hormonal homeostasis [30] as well as possible skin damage [31]. The applicability of WBH was checked against the list of contraindications such as severe cerebral perfusion deficiency, cardiac arrhythmias and heart failure, uncontrolled hyperthyroidism, pregnancy, acute severe infections, manifest internal organ failure, reduced or increased thermo-sensitivity of the skin and acute thermal skin damage (sunburn) [30]. WBH was mainly recommended to patients who reported positive experience with previous heat applications, while WBH was not scheduled for patients who were averse to heat exposure. The PCS diagnosis was based on the diagnostic criteria defined in the NICE and German AWMF guidelines [3,4]. All patients underwent detailed medical history taking, physical examination and laboratory diagnostics and, if required, medical imaging, pulmonary function tests and psychological diagnostic evaluation. This comprehensive diagnostic work-up served to substantiate the diagnosis of PCS and to distinguish patients with symptoms similar to PCS but attributed to other diseases. The criteria that led to the exclusion of data from the study analysis included severe comorbidities with PCS-like symptoms such as advanced oncological, respiratory, or cardiovascular diseases with progressive fatigue or dyspnea, advanced neurological diseases with cognitive impairment or fatigue, and symptomatic endocrine diseases (e.g., manifestations of hypothyroidism).

2.2. Interventions

All patients with PCS received a multimodal therapy that included IM approaches in addition to conventional medicine. In addition, the patients were treated with at least one and a maximum of three applications of fever-range WBH with a heckel-HT3000 device (Hydrosun Medizintechnik GmbH, Müllheim, Germany) using water-filtered infrared-A (wIRA) irradiation or a heckel-HT2000 device (Heckel Medizintechnik GmbH, Esslingen, Germany) using diffuse reflection-scattered infrared-A/-B irradiation. The WBH unit is installed in a separate room. During WBH, the patient lies in a heating chamber that is heated by infrared radiators. The patient is awake and responsive throughout the procedure. A specially trained nurse accompanies the patient through the procedure, checks vital signs and, if required, hands out beverages in the heating chamber. The head section of the heating chamber is transparent so that the patient can maintain visual contact with their surroundings. The WBH procedures each lasted about three hours. After an irradiation phase up to a target core body temperature (rectal measurement) of 38.8–39.8 °C, depending on the patient's tolerance, the infrared lights were partially turned off and the patients remained in a recumbent

position in the heckel device. The patients were then transferred back to the ward and remained wrapped in blankets for another two hours to slowly cool down. The WBH interventions were administered shortly after admission to hospital and then at intervals of approximately three days.

Drug therapy and IM therapeutic interventions were tailored to the individual needs of the patients according to an in-house guideline and included herbal and anthroposophic remedies, art therapy (e.g., painting), eurythmy therapy, physiotherapy, rhythmical massage, and local heat applications by means of compresses and wraps [32–34]. In addition, mistletoe was used because of its beneficial immunomodulatory effect [35,36].

2.3. Outcome measures

The data for the outcome measures were collected at hospital admission (T0 = baseline), at discharge (T1) and four weeks after discharge (T2 = follow-up). The primary outcome measure was the change in the sum score of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) questionnaire [37,38] between T0 and T2. The secondary outcome measures included changes in the sum scores of the Fatigue Impact Scale (FIS-D) [39–41], Multidimensional Dyspnea Profile (MDP) [42–44] and Covid-Associated Symptoms (CAS) (Supplementary Table S1) questionnaires between T0–T1, T0–T2 and T1–T2, as well as changes in the sum score of the FACIT-F between T0–T1 and T1–T2.

2.4. Study instruments

The FACIT-F fatigue scale is a 13-item questionnaire to assess an individual's level of fatigue during their usual daily activities and function over the past 7 days [37]. The response to each item is recorded on a five-point Likert-type scale (0 = not at all to 4 = very much) and the total scale range is 0–52, with higher scores representing less fatigue (after recoding of negatively worded item responses) [38]. The internal consistency of the FACIT-F is high, with a Cronbach's coefficient α exceeding 0.90 [37]. In this study, we used the German version of the FACIT-F, the reliability and validity of which had previously been confirmed [38].

The FIS-D fatigue impact scale is an internationally used instrument for assessing the impact of fatigue on physical (10 items) and cognitive (10 items) performance as well as psychosocial functioning (20 items) within the previous month on a 5-point Likert scale (0 = no problem to 4 = extreme problem). The total sum score of the FIS-D ranges from 0 to 160, with higher scores indicating increased levels of self-perceived fatigue [39,40]. The German version of the FIS-D was validated and demonstrated a high internal consistency for the total score and the three subscales (Cronbach's $\alpha = 0.94–0.96$) and a high test–retest reliability (0.72–0.83) [41]. As the questions refer to a recall period of 4 weeks/1 month, we used the questionnaire at T0 and T2 (start of inpatient treatment and 4 weeks after discharge), but not at T1 (discharge).

The MDP is a validated instrument developed to assess multiple sensory and affective sensations of breathlessness [42]. It is comprised of 11 items, each rated on a numerical scale from 0 to 10, with higher scores indicating more severe breathlessness. The 11 items cover three areas: general discomfort due to breathlessness (A1; one item), sensory qualities describing breathlessness (SQ; 5 items), and possible emotional responses related to breathlessness (A2; 5 items). The MDP has been translated into several languages, including French, Turkish, Swedish, Portuguese and German [43]. Psychometric properties meet the standards for internal consistency reliability (Cronbach's $\alpha = 0.89$ and 0.82 for sensory and emotional dimensions, respectively) and test-retest reliability (intraclass correlations = 0.84 and 0.86 for immediate perception and emotional scores, respectively) [44].

In addition, a self-developed, study-specific questionnaire 'Covid-Associated Symptoms' (CAS) was used to assess the extent of other symptoms such as insomnia, depressed mood, loss of appetite and post-exertional malaise. The questionnaire contained 12 items about persistent cough, muscle and limb pain, headaches, anxiety, sleep disorders, chest pain, heart complaints such as tachycardia or palpitations, loss of appetite, post-exertional malaise, and breathlessness at rest and during physical exertion. Patients were asked to rate each item on a five-point Likert scale (0 = not at all, 4 = very strongly, indicating poorer health) (Supplementary Table S1). At T2, patients were also asked, using an open-ended question, which therapeutic IM intervention they felt had contributed most to improving their PCS symptoms.

2.5. Data collection

The data were collected via medical record review at the Paracelsus Hospital Unterlengenhardt between February and December 2021. Data collection included age, gender, symptoms, PCS diagnosis, interventions received during hospitalization, number of treatments with WBH and maximum temperature during WBH treatment. Patients were also asked to complete a set of paper questionnaires for each time-point (T0, T1, T2). The statistical analysis was carried out by the ARCIM Institute (Academic Research in Complementary and Integrative Medicine) in Filderstadt, Germany. The ARCIM Institute received the data in anonymized form.

2.6. Statistical analysis

The statistical analysis was conducted using R (version: 4.4.2) [45] and RStudio (version: 2024.12.0.467) [46]. The demographic data were presented descriptively, with continuous variables expressed as mean ± standard deviation and categorical or binary data expressed as absolute and relative frequencies. Before analyses were carried out, the data were checked for their distribution and analyzed accordingly. A paired *t*-test was performed for the primary outcome, the change in the FACIT-F sum score between T0 and T2. For the secondary outcome parameters, mean ± standard deviation, mean differences with corresponding effect sizes (Cohens *d*, R package: effsize [47]) and 95% confidence intervals (95CI) were calculated. Missing values were imputed by multiple imputation by chained equations (MICE) (R package: mice [48]) and the pooled statistics were calculated (R package: MKmisc [49]). In terms of a sensitivity analysis, the calculation was performed without and with imputation of missing values. A p-value below 0.05 was considered statistically significant.

3. Results

3.1. Study population

Between February and December 2021, 94 patients were admitted to the Paracelsus Hospital Unterlengenhardt for inpatient treatment of PCS. Of these, 48 were excluded from data analysis because they had returned the questionnaires incompletely (not suitable for missing imputation analysis) ($n=18$) or not at all ($n=10$), because they did not meet the diagnostic criteria for PCS ($n=10$), because the primary diagnosis was other than PCS ($n=4$), because they did not have a confirmatory COVID-19 test at the time of infection ($n=3$) or because they had not received WBH ($n=3$). The final sample included data from 46 patients with a mean age of 50.0 years ($SD=13.0$), the majority of whom were women ($n=40$, 87.0%). More than 80% of patients responded at follow-up (details given in Supplementary Table S2). All patients were discharged during the study period. None of them reported further COVID-19 infections prior to the one that led to PCS or other respiratory infections shortly before hospitalization. Vaccination status was not collected, which is a shortcoming of the dataset discussed as a limitation. The duration of inpatient treatment was nine days for all patients, in accordance with the German DRG system (Diagnosis Related Groups), which stipulates nine days as the maximum length of stay for patients with PCS who do not require 24 h-monitoring, which was not the case in the study sample. Patients were discharged if no serious deterioration had occurred during their hospital stay and their condition was stable enough to allow them to return to their home environment. Of the patients whose data were included in the study analysis, none were readmitted for a second round of treatment. The main symptoms experienced by patients during the acute COVID phase were pain ($n=42$, 91.3%), fatigue ($n=33$, 71.7%) and respiratory symptoms ($n=32$, 69.6%). During the acute COVID-19 phase, 67.4% ($n=31$) of patients had a fever with an average maximum body temperature of 38.9 ± 0.8 °C (Table 1 and Supplementary Table S3). On admission to hospital, the main persistent debilitating PCS symptoms were fatigue ($n=43$, 93.5%), pain ($n=28$, 60.9%) and respiratory symptoms ($n=25$, 54.3%) (Table 1 and Supplementary Table S3).

In addition to the confirmed PCS diagnosis in all patients whose data were included in the study analysis, further diagnostic examinations revealed additional health conditions. The most frequent secondary diagnoses included diseases of the circulatory system (ICD I00–I99, $n=7$, 15.2%), mental and behavioral disorders (ICD F00–F99, $n=6$, 13.0%) and endocrine/metabolic disorders (ICD E00–E90, $n=5$, 10.9%). The most prevalent tertiary diagnoses included endocrine/metabolic disorders (ICD E00–E90, $n=6$, 13.0%), musculoskeletal and connective tissue disorders (ICD M00–M99, $n=5$, 10.9%) and diseases of the circulatory system (ICD I00–I99, $n=4$, 8.7%) (Table 1 and Supplementary Table S4).

Most patients ($n=37$, 80.4%) received two WBH treatments (three days apart), with a few receiving one ($n=6$, 13.0%) or up to three ($n=3$, 6.5%) (Table 2).

Details on IM medications and non-medication therapies are given in the Supplementary Table S5.

Table 1. Demographic and baseline characteristics of the patients.

		n (%) / Mean ± *SD*
Gender		
	Female	40 (87.0%)
Age (years)		
	Mean ± *SD*	50.0 ± 13.0
Test method (SARS-CoV-2)		
	PCR	40 (87.0%)
	Antibody	4 (8.7%)
	Other	2 (4.3%)
Fever during acute COVID-19[a]		
	Yes	31 (67.4%)
Maximum fever temperature (°C)[b]		
	Mean ± *SD*	38.9 ± 0.8
Antipyretic medication during acute COVID-19[c]		
	Ibuprofen	14 (30.4%)
	Acetaminophen	13 (28.3%)
	Acetylsalicylic Acid	5 (10.9%)
	Metamizole	3 (6.5%)
	None	11 (23.9%)
Main symptoms[d]		
During acute COVID-19		
	Pain	42 (91.3%)
in the muscles and joints: 22/42 (47.8%)		
	Fatigue and weakness	33 (71.7%)
	Respiratory symptoms	32 (69.6%)
On hospital admission		
	Fatigue and weakness	43 (93.5%)
	Pain	28 (60.9%)
in the muscles and joints: 14/28 (30.4%)		
	Respiratory symptoms	25 (54.3%)
Diagnoses[d]		
Secondary diagnoses according to ICD-10 (diseases of …)		
The circulatory system (I00–I99) (e.g., hypertension, acute myocardial infarction)		7 (15.2%)
Mental and behavioral disorders (F00–F99) (e.g., depressive disorder single/ recurrent)		6 (13.0%)
Endocrine, nutritional and metabolic (E00–E90) (e.g., hypothyroidism, thyrotoxicosis)		5 (10.9%)
Tertiary diagnoses according to ICD-10 (diseases of …)		
Endocrine, nutritional and metabolic (E00–E90) (e.g., hypothyroidism, autoimmune thyroiditis)		6 (13.0%)
The musculoskeletal system and connective tissue (M00–M99) (e.g., pain in right knee, sicca syndrome)		5 (10.9%)
The circulatory system (I00–I99) (e.g., rheumatic tricuspid insufficiency, hypertension)		4 (8.7%)

Note. Missing values (%): [a] = *4 (8.7%)*; [b] = *18 (39.1%)*; [c] = *9 (19.6%)*.
[d]A maximum of the three most frequent cases are listed here; a comprehensive list is available in the Supplementary Table S4.

3.2. Primary outcome

For the primary outcome measure, we found a statistically significant ($p<0.001$) increase in the FACIT-F sum score between T0 (19.5 ± 8.4) and T2 (29.6 ± 13.0) with a mean

Table 2. WBH treatments performed during the patients' hospitalization.

		n (%) / Mean ± *SD*
Number of WBH treatments		
	2	37 (80.4%)
	1	6 (13.0%)
	3	3 (6.5%)
Fever temperature (>=38.5 °C) reached during WBH[a]		
	Yes	31 (67.4%)
Maximum temperature during WBH[a]		
	Mean ± *SD*	38.7 ± 0.6
Number of patients who rated WBH as effective[b]		
	WBH	19/30 (63.3%)

Note. Missing values (%): [a] = *1 (2.2%)*. [b] In the expression *n/N* (%), '*n*' represents the number of responses, '*N*' denotes the total number of responses in the full cohort, and the percentage is calculated based on the response rate.

Table 3. Primary and secondary outcomes of the study.

	Mean ± SD			ΔMean (95% CI); Cohen's *d*		
	Admission (T0)	Discharge (T1)	Follow-Up (T2)	T1 vs T0	T2 vs T0	T2 vs T1
Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)[High]						
Total Sum Scores	19.6 ± 8.6	31.0 ± 10.9	29.2 ± 12.8	**11.4**(8.2,14.5);d = 1.2	**9.6**(5.8,13.3);d = 0.9	−1.8(-5.3,1.7);d = 0.2
Fatigue Impact Scale (FIS-D)[±]						
Total cognitive	26.7 ± 8.0	–	23.4 ± 9.0	–	**−3.3**(-5.8,-0.9);d = 0.4	–
Total physical	28.6 ± 4.8	–	23.5 ± 9.2	–	**−5.1**(-7.6,-2.5);d = 0.7	–
Total social	48.5 ± 13.0	–	40.7 ± 18.5	–	**−7.8**(-11.9,-3.6);d = 0.5	–
Total	103.8 ± 22.2	–	87.6 ± 35.1	–	**−16.2**(-24.3,-8.1);d = 0.6	–
Multidimensional Dyspnea Profile (MDP)						
Sensory quality domain	16.4 ± 13.5	10.5 ± 9.8	13.3 ± 13.0	**−5.8**(−9.3,−2.4);d = 0.5	−3.1(−7.5,1.3);d = 0.2	2.8(−1.2,6.8);d = 0.2
Immediate perception score	20.6 ± 15.4	13.1 ± 11.3	16.7 ± 15.0	**−7.5**(−11.5,−3.6);d = 0.6	−3.9(−9.0,1.3);d = 0.3	3.7(−1.0,8.3);d = 0.3
COVID-Associated Symptoms (CAS)						
Persistent cough	0.5 ± 0.8	0.4 ± 0.8	0.7 ± 1.0	−0.2(−0.4,0.1);d = 0.2	0.1(−0.1,0.4);d = 0.2	**0.3**(0.0,0.6);d = 0.3
Muscle and limb pain	2.0 ± 1.5	1.5 ± 1.4	1.9 ± 1.4	**−0.5**(−0.9,−0.1);d = 0.3	−0.1(−0.6,0.4);d = 0.1	0.3(−0.2,0.8);d = 0.2
Headaches	1.9 ± 1.2	1.4 ± 1.1	1.5 ± 1.4	**−0.5**(−0.9,−0.1);d = 0.4	−0.4(−0.9,0.1);d = 0.3	0.1(−0.4,0.6);d = 0.1
Depressed mood	1.9 ± 1.3	1.2 ± 1.2	1.2 ± 1.3	**−0.7**(−1.1,−0.4);d = 0.6	**−0.7**(−1.1,−0.2);d = 0.5	0.1(−0.4,0.6);d = 0.1
Anxiety	1.5 ± 1.4	0.7 ± 1.0	0.9 ± 1.3	**−0.9**(−1.3,−0.4);d = 0.7	**−0.6**(−1.1,−0.1);d = 0.4	0.3(−0.2,0.7);d = 0.2
Sleep disorders	2.1 ± 1.3	1.9 ± 1.3	1.9 ± 1.3	−0.2(−0.7,0.3);d = 0.2	−0.2(−0.7,0.2);d = 0.2	−0.0(−0.6,0.5);d = 0.1
Chest pain	1.2 ± 1.3	0.7 ± 0.9	1.0 ± 1.1	**−0.5(−**0.8,−0.1);d = 0.4	−0.2(−0.6,0.2);d = 0.2	0.3(−0.1,0.6);d = 0.3
Heart complaints	1.6 ± 1.3	1.1 ± 0.9	1.1 ± 1.1	**−0.5**(−0.9,−0.1);d = 0.4	−0.4(−0.9,0.0);d = 0.4	0.0(−0.3,0.4);d = 0.1
Loss of appetite	0.6 ± 1.1	0.5 ± 0.8	0.6 ± 0.9	−0.2(−0.5,0.1);d = 0.2	−0.1(−0.4,0.3);d = 0.1	0.1(−0.2,0.4);d = 0.1
Post-exertional malaise	2.9 ± 1.2	1.8 ± 1.4	2.2 ± 1.4	**−1.1**(−1.5,−0.6);d = 0.8	**−0.6**(−1.1,−0.2);d = 0.5	0.4(−0.1,0.9);d = 0.3

Note. Unless otherwise specified, lower values represent better health. [High]Higher values represent better health. [+] The data was collected only at T0 and T2. **Bold** indicates significant values.

increase of 10.1 (95CI: 7.1–14.2) and a large effect size ($d = 0.9$) (results without missing imputation). For the sensitivity analysis, a second calculation was performed using MICE (Table 3). The results were similar to those without MICE, which indicates robust results.

3.3. Secondary outcomes

Regarding fatigue, a statistically significant increase in the FACIT-F sum score was observed between T0 (19.6 ± 8.6) and T1 (31.0 ± 10.9) with a large effect size (Δm = 11.4; 95CI: 8.2,14.5; $d = 1.2$), indicating lower levels of self-reported fatigue. The average total FIS-D score decreased significantly between T0 (103.8 ± 22.2) and T2 (87.6 ± 35.1) (Δm = −16.2; 95CI: −24.3, −8.1; $d = 0.6$) indicating lower levels of self-perceived fatigue. The significant decrease in the FIS-D revealed the largest effect size for the physical domain (Δm = −5.1; 95CI: −7.6, -2.5; $d = 0.7$), followed by the social domain (Δm = −7.8; 95CI: −11.9, −3.6; $d = 0.5$) and the cognitive domain (Δm = −3.3; 95CI: −5.8, −0.9; $d = 0.4$).

Concerning dyspnea, the total MDP score for immediate perception (sum of A1 and SQ scores) decreased significantly (Δm = −7.5; 95CI: −11.5, −3.6; $d = 0.6$) from 20.6 ± 15.4 at T0 to 13.1 ± 11.3 at T1. Similarly, a significant reduction in the total score of the sensory quality domain (SQ) (Δm = −5.8; 95CI: −9.3, −2.4; $d = 0.5$) was observed between T0 (16.4 ± 13.5) and T1 (10.5 ± 9.8). However, there was no statistically significant decrease in MDP scores between T0 and T2.

The CAS questionnaire showed a statistically significant improvement for depressed mood (Δm = −0.7; 95CI: −1.1, −0.4; $d = 0.6$), anxiety (Δm = −0.9; 95CI: −1.3, −0.4; $d = 0.7$) and post-exertional malaise (Δm = −1.1; 95CI: −1.5, −0.6; $d = 0.8$) between T0 and T1 as well as between T0 and T2, here with a medium effect size ($d = 0.5$).

Results for the secondary outcomes are presented in Table 3 (with MICE). For the sensitivity analysis, a second calculation was performed without MICE. The results were similar to those with MICE, which indicates robust results.

Patient feedback on the therapeutic effect of IM treatments showed that 63.3% of respondents named WBH as the most effective treatment within the multimodal IM therapy concept (Table 2). The analysis of WBH patient feedback is based on $n = 30$ (out of a total sample of $n = 46$) responses, as not all patients responded to the question about their rating of the treatment approaches. The response data on the other approaches, such as nursing applications, art therapy, eurythmy therapy and rhythmical massage, are unspecific and incomplete and do not allow any quantitative conclusions to be drawn, which is discussed as a limitation of the study.

Adverse events related to WBH occurred in two cases. Two patients reported migraine-like headaches and circulatory disturbances after WBH. For one, the symptoms occurred after the first WBH treatment, for the other after the second. Both patients did not receive any further WBH treatment and received symptom-oriented naturopathic treatment. The symptoms subsided after one to two days.

4. Discussion

This study provides preliminary evidence for the effectiveness of an inpatient multimodal therapeutic approach including WBH for PCS symptoms of fatigue, dyspnea, depressed mood, anxiety, post-exertional malaise and palpitations. Statistically significant improvements were seen for the FACIT-F sum score, the FIS-D sum score and all three subscores as well as for depressed mood, anxiety, and post-exertional malaise at hospital discharge (T1) and at the 4-week follow-up (T2). Regarding dyspnea, significant improvements were observed at T1.

Our results are consistent with other studies that have investigated the effects of various interventions on PCS symptoms such as fatigue, dyspnea, and depression. In a 2021 case report, enhanced external counterpulsation (EECP) was found to have a beneficial effect on a patient with PCS by alleviating fatigue, dyspnea, body pain and 'brain fog'. EECP uses mechanical compression exerted by compressive cuffs wrapped around the calves, thighs and buttocks that inflate and deflate specifically timed to the patient's electrocardiogram. The rhythmic compression induces physiological and biochemical changes that are assumed to improve systemic endothelial function [50]. Exercise training rehabilitation with two sessions per week over a period of 90 days was found to be effective in relieving dyspnea in patients with persistent respiratory discomfort after COVID-19-related acute respiratory distress syndrome (CARDS) [51]. Jimeno-Almazán et al. conducted a four-arm RCT and reported that eight weeks of concurrent training with or without inspiratory muscle exercise was more effective in improving PCS symptoms such as dyspnea, fatigue and depression than the WHO self-management recommendations and inspiratory muscle training alone [52]. Other studies have reported on the potential rehabilitative role of inspiratory muscle training in improving exercise capacity, peak oxygen consumption, quality of life and dyspnea [53,54]. With regard to nutraceuticals, Tosato et al. reported the effectiveness of L-arginine plus vitamin C in alleviating symptoms of fatigue in PCS, possibly by stimulating the synthesis of nitric oxide, which improves the immune response as well as endothelial and muscle function [55].

WBH is a technique that has proven effective in the treatment of cancer [21,27], depression [25,56] and fibromyalgia [23,57], among others. Published clinical data on the efficacy of WBH in PCS are scarce. Our findings in this regard are consistent with a case report published by Romeyke in 2022 [29], in which the author reports on the role of WBH in improving the physical well-being and mental state of a patient whose PCS was accompanied by pronounced fatigue, sleep disorder, inner restlessness and depression [29]. Temperatures in the fever range (38-41 °C) can influence both the innate and the adaptive immune response [58]. Elevated temperatures can promote the transport of immune cells and thus support immune surveillance during infection [59]. A rapid SARS-CoV-2-specific T cell response is important because Th1 helper cells derived from $CD4^+$ T cells are able to produce cytokines and recruit innate immune cells, giving Th1 cells a direct antiviral function [60]. This process has been associated with rapid control of viral infection and mild disease progression in COVID-19, as described by Tan, Linster et al. [61]. Virus-specific CD4 T cells are also involved in tissue repair via the production of interleukin-22 (IL-22) [60]. *In vitro* studies have shown that temperatures between 38.5 and 39.5 °C promote the differentiation of Th17 helper cells from naïve $CD4^+$ T cells and increase the expression of IL-17 and IL-22 [62]. A beneficial effect of WBH on the mental state was also found in patients with fibromyalgia, as well as a reduction in self-reported pain intensity and an improvement in functional capacity [24,57].

In a recent review, Smadja and Abreu [22] outline the key pathophysiological features of neurodegenerative diseases and long COVID and open up new perspectives for WBH as a potential and potent innovative treatment option for these conditions. The authors describe the role of WBH in the induction of heat shock proteins (HSPs), the regulation of serotonin levels and the enhancement of mitochondrial function. HSPs are essential for the folding, repair and degradation of proteins and can exert cytoprotective effects. Serotonin is an important neurotransmitter involved in a variety of physiological processes, such as stress response, cognitive function, thermoregulation, sleep and mood regulation. Mitochondrial function is vital for energy production. Dysfunction of the mitochondria contributes to fatigue, a key symptom in PCS, through increased oxidative stress and impaired energy production. While the exact modes of action are still to be revealed, Smadja and Abreu suggest a possible beneficial interaction between WBH, mitochondrial and serotonin dysregulation and HSPs in persistent COVID-19 conditions. Emphasis is also placed on the dual nature of WBH effects, which have the potential to trigger both anti-inflammatory and pro-inflammatory responses, requiring precisely controlled application of WBH and close patient monitoring [22]. In our study, the patients received WBH alongside therapies from IM, mainly from anthroposophic medicine. In addition to conventional medicine, the therapy concept comprised medications from phytotherapy and AM, nursing applications (compresses, embrocations) and non-medication therapies such as eurythmy therapy, physical therapy, rhythmical massage and art therapies (painting, sculpting, music therapy). AM is an integrative, multimodal therapy system developed by Rudolf Steiner and Ita Wegman in the early 1920s on the basis of a holistic understanding of organism, illness and therapy [32–34]. Eurythmy therapy as a special component of AM is a mindful movement therapy [63]. AM medications are derived from plants, minerals, animals and chemically defined substances [64]. AM therapies were selected for their beneficial effects on the immune system [65], mood [66,67], fatigue [63] and chronic pain [34,68]. However, the discussion about AM in the relevant literature is controversial and underlines the need for further robust research [33,69].

With regard to multimodal therapy, data on medication was only available in 57% of all cases (26/46) and on non-medication therapies and nursing applications in 43% (20/46, Supplementary Table S5), which represents a limitation of our study. Furthermore, in the few cases for which data were available, the distribution of therapies was quite heterogeneous. In contrast, WBH was applied in all included cases and 63% of patients gave positive feedback. Quantification of patient feedback on the other therapy approaches, such as art therapy, eurythmy therapy and nursing applications, was not possible due to the unspecific and incomplete response data.

We therefore decided not to include the data on medication, non-medication therapies and nursing applications in our study analysis. Information on these IM therapies is detailed in the Supplementary Table S5. Given the paucity of studies and recognized guidelines for the treatment of PCS at the time of our study and in view of the multiple symptoms associated with the condition, implementing a multimodal therapeutic strategy appeared justified in the clinical context. However, as the potential contributions of the individual therapy components cannot be clearly quantified, we have focused our analysis mainly on the WBH data. According to the patients' rating of the effects of the different therapy approaches, WBH had contributed the most to alleviating PCS symptoms.

Another limitation of the present study is that the analyzed data originated from a retrospective review of the information collected during the hospital stay, which led, in part, to incomplete data sets such as the FIS-D data at T1.

The retrospective nature and the fact that the study did not include a control group limit the generalizability of the results. Furthermore, the results of the study were based on self-report and not substantiated by measurements of physiological parameters. Currently, there are no physiological or laboratory parameters that are capable of measurably reflecting the severity of self-perceived PCS symptoms and possible changes in symptom burden [4]. In addition, the study included patients who had a range of heterogeneous secondary and tertiary diagnoses, the impact of which is difficult to determine. Vaccination status was not collected, which is a shortcoming of the dataset, as the information could have contributed to the ongoing research on the impact of vaccination on the development of PCS [70,71]; however, it should be noted that study data collection began in February 2021, when the vaccine had only recently been introduced and was not widely available to all people. A potential for selection bias should also be mentioned. Since the study data were collected in an anthroposophic hospital, patients may have already been open to alternative therapies, which could skew the perception of effectiveness.

With regard to the duration of treatment effects, parameters were collected at discharge and four weeks after discharge. While for most CAS items the effects only persisted in cases where at least medium effect sizes were observed between T1 and T0, a significant effect was only observed for the MDP parameters between T1 and T0, but no longer four weeks after discharge. In contrast, high effect sizes were observed for the primary outcome parameter (FACIT-F sum score) both between T1 and T0 and between T2 and T0. Nevertheless, it must be mentioned as a limitation that no information is available for a longer-term follow-up period, e.g., of 3, 6 or 12 months. It would be desirable for future studies to find out which patients benefit from a single clinical stay and for which a second stay would be necessary to boost the therapeutic effects.

5. Conclusions

In conclusion, our results provide preliminary evidence that WBH is generally well tolerated by patients with PCS and is predominantly positively evaluated. In future studies, especially if WBH is embedded in multimodal therapy approaches, the sample sizes should be large enough to allow for subgroup analyses and thus to identify possible specific effects of individual treatment components.

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Author contributions

Conceptualization, Jan Vagedes, Jan Mergelsberg; Data curation, Jan Mergelsberg, Victoria Heinrich and Mohammad Islam; Formal analysis, Jan Vagedes and Mohammad Islam; Funding acquisition, Jan Mergelsberg; Investigation, Jan Mergelsberg, Thomas Breitkreuz and Victoria Heinrich; Methodology, Jan Vagedes, Jan Mergelsberg and Thomas Breitkreuz; Project administration, Jan Mergelsberg; Resources, Jan Vagedes, Jan Mergelsberg and Thomas Breitkreuz; Software, Jan Vagedes and Mohammad Islam; Supervision, Jan Mergelsberg, Jan Vagedes, Mohsen Sobh and Katrin Vagedes; Validation, Jan Vagedes, Mohammad Islam, Katrin Vagedes and Jan Mergelsberg; Visualization, Jan Vagedes, Mohsen Sobh, Mohammad Islam and Katrin Vagedes; Writing – original draft, Mohsen Sobh, Jan Vagedes and Katrin Vagedes; Writing – review & editing, Jan Vagedes, Katrin Vagedes, Thomas Breitkreuz, Victoria Heinrich and Jan Mergelsberg.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Registration

DRKS - Deutsches Register Klinischer Studien, DRKS00033018, retrospectively registered on 13.11.2023

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Baden-Württemberg Medical Association, approval number F-2023-106. As the study is a retrospective data analysis, no written informed consent was obtained.

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Data availability statement

Data will be made available upon reasonable request to the corresponding author.

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