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Case Report

Whole-Body Cryostimulation: A Rehabilitation Booster in Post-COVID Patients? A Case Series

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Abstract: Given the severity and prevalence of post-COVID-19 symptoms in the general population, the identification of boosters for rehabilitation programs appears to be of paramount importance. The purpose of this case series is to provide some preliminary evidence about the role of whole-body cryostimulation (WBC) as an effective adjuvant for the recovery of patients with the post-COVID-19 condition (PCC). We recruited seven patients with previously confirmed SARS-CoV-2 infection and symptoms of PCC of different severities for a comprehensive rehabilitation program, including WBC. The main symptoms were dyspnea, chronic and muscular fatigue, chronic pain, and poor sleep quality. Moreover, some patients presented high levels of hematological markers of inflammation. Because we provided a range of interventions, including nutritional and psychological support along with physical exercise and physiotherapy, we could not determine to what extent WBC may *per se* have accounted for the clinical and functional improvements. However, for all reported cases, it was observed that the introduction of WBC sessions represented a turning point in the patient's subjective and objective improvements related to health and functioning.

Keywords: whole-body cryostimulation; rehabilitation; post-COVID

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1. Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, and the globally confirmed case count of COVID-19 surpassed 290 million in January 2022 (World Health Organization, n.d.). Despite pulmonary impairments being the most prevalent, extra-pulmonary manifestations of COVID-19 are abundant, involving psychosocial, cardiovascular, hematologic, renal, gastrointestinal, and central nervous system symptoms, as well as post-intensive care syndrome. COVID-19 causes a strong pro-inflammatory cytokine storm, which can often persist also in the subacute phase and can lead to muscular complications such as critical illness myopathy (CIM) [1], and acute sarcopenia [2]. The long-term implications of the 'post-COVID-19 condition' (PCC) [3], defined as persistent symptoms usually occurring 3 months from the onset in individuals with a past confirmed or probable SARS-CoV-2 infection, persisting for at least 2 months, and which cannot be explained by an alternative diagnosis, still remain to be fully uncovered [4–7]. The most frequently reported symptoms are musculoskeletal (fatigue and muscle aches) and psychological (concentration and memory deficit, depression, and anxiety), and also include

dyspnea, persistent cough, fever, and loss of smell or taste [3,4,6,8]. More than 30% of individuals affected by COVID-19, including asymptomatic cases, and approximately 80% of patients hospitalized for COVID-19 have PCC symptoms [4,9]. SARS-CoV-2 patients require intensive multidisciplinary rehabilitation, aimed at restoring independence in basic daily activities [10]. In contrast to other self-limiting symptoms (e.g., anosmia) [11], fatigue and cognitive impairment appear to endure or even worsen in susceptible individuals [12]. Rehabilitation guidelines for PCC patients have been released by the World Health Organization, Cochrane Rehabilitation launched REH-COVER, and there are continuous updates in the scientific community on rehabilitation best practices for these patients [9,13,14]. Physiotherapy and resistance training integrated with nutritional interventions, along with reduction in the inflammatory state, is key to regaining independence in PCC patients. Whole-body cryostimulation (WBC) exposes patients to cryogenic temperatures, ranging from −110 °C to −140 °C, in an environmentally controlled cabin for 2–3 min. Such stimulus induces pain and inflammatory status reduction in different conditions [15–18] and induces improvements in depression, anxiety [19], functional status and fatigue [20], and quality of sleep [21]. It is widely used as a recovery technique after physical exercise in elite athletes [22] and the positive effects of 10 serial WBC sessions on PCC patients have been reported 1 month after discontinued treatment [23]. The broader existing evidence of clinical and functional benefits following WBC in musculoskeletal and neurological conditions provides a rationale for prescribing WBC for post-COVID symptoms. To the best of our knowledge, only one study to date has investigated the effects of WBC on post-COVID musculoskeletal and respiratory symptoms [2]. Therefore, the main focus of this case series was to provide preliminary evidence about the role of whole-body cryostimulation (WBC) as an effective adjuvant for the recovery of patients with the post-COVID condition (PCC).

2. Materials and Methods

2.1. Participants, Inclusion and Exclusion Criteria

We consecutively recruited 7 patients from August 2021 to January 2022 who were referred to our rehabilitation unit (RU) for a comprehensive rehabilitation program after a SARS-CoV-2 infection. All patients presented with different sequelae of post-COVID symptoms and a clinical picture compatible with PCC. In addition, 6 of the 7 patients also had an obesity condition (BMI > 30 kg/m^2). Symptoms primarily reported were dyspnea and chronic fatigue, chronic pain, muscular fatigue, reduced quality of life, and worsening sleep quality. Some of the patients also had high levels of hematological markers of inflammation. Before admission to our hospital, patients had to present two consecutive negative swabs for SARS-CoV-2. The only inclusion criterion was post-COVID status; no age restriction was applied. The exclusion criteria only included the contraindications to WBC treatment listed in Appendix A [24] and were evaluated upon admission by a physician who examined the patients.

2.2. Whole-Body Cryostimulation Procedure

Patients underwent a WBC cycle consisting of 10 sessions over a period of two weeks. Patients minimally dressed, wearing a surgical mask, ear band, gloves, t-shirt, shorts, socks, and plastic clogs, were first acquainted with the cryochamber (Artic, CryoScience, Rome, Italy) during a first WBC 1-min session at −110 °C. Before entering the cryochamber (Figure 1), glasses, contact lenses, and metallic jewelry were removed and the body thoroughly dried. Constant vocal and eye contact with the patient was maintained during the whole session by properly qualified personnel.

Figure 1. Example of the cryostimulation session (**left**). Cryochamber (CryoScience, Rome, Italy) (**right**).

2.3. Rehabilitation Program

All participants followed a specific timeline (Figure 2) undergoing:

a. A personalized nutritional program based on the patient's nutritional history and the assessment of the resting energy expenditure. The optimal total daily intake and diet composition were defined by a clinical dietitian within the Istituto Auxologico Italiano. All patients were advised to continue the same diet after the discharge.

b. Two 60-min daily physiotherapy sessions including personalized progressive aerobic training, postural control, and progressive strengthening exercises supervised by a physiotherapist. Aerobic sessions were monitored with the subjective perception of fatigue (Borg's CR10 scale), and oxygen saturation (SpO2). Exercises were stopped when a score of 5 on the Borg scale was reached. The first aerobic session performed in the morning after WBC consisted of walking at a self-selected cadence. The second session performed in the afternoon consisted of arm-cranking at an intensity of 65% of HRmax according to the Karvonen equation ((220 − age) × 0.65). This approach was individualized according to the patient's fitness, clinical status, and subjective perception of fatigue. Joint mobility and body weight strengthening exercises were performed according to the individual fitness level.

c. A WBC cycle (10–15 sessions at −110 °C from Monday to Friday, at 8:15 A.M., before physical exercise classes and physiotherapy) using a cryochamber (Artic, CryoScience, Rome, Italy) (Figure 1). The safety profile of the device for both pulmonary [25] and cardiac function [26] had been previously demonstrated, and no adverse effects were reported under the conditions of use indicated. The first WBC session lasted 1 min at −110 °C to familiarize the patient with the cryochamber temperature, whereas all following treatments lasted 2 min. The patient's skin surface temperature was measured before and after each treatment with an infrared thermometer (Fluke Corporation, Everett, WA, USA) at the neck, quadriceps, popliteal fossa, and calf level.

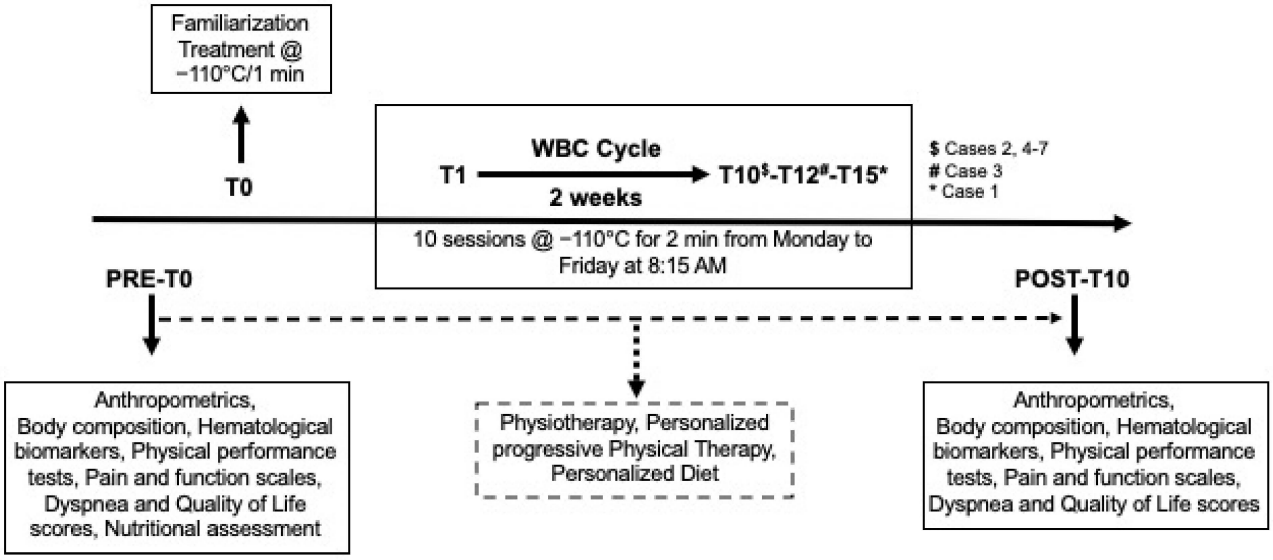

Figure 2. Timeline for study participants.

2.4. Outcome Measures

Anthropometrics, body composition, hematological biomarkers, and physical performance tests were measured before and after the completion of the rehabilitation program (on average 30 days) with the final evaluations performed 5–7 days after the last WBC session. No follow-up measurements were performed after discharge.

Anthropometric measurements included weight, height, body mass index (BMI), and waist circumference (WC), whereas body composition parameters included fat mass (FM), free fat mass (FFM), muscle mass (MM), and appendicular skeletal muscle mass (ASMM). These were assessed by bioelectrical impedance analysis (BIA 101/s, Akern®, Florence, Italy).

Blood samples were drawn in the morning under fasting conditions. The hematological biomarkers that were analyzed included ALT, AST, GGT, HBA1c, glucose, insulin, total cholesterol, HDL, LDL, TG, ferritin, CPR, ESR, and LDH.

Physical performance tests included: a 6-min walking test (6MWT), a handgrip test of the dominant arm, and the Timed Up and Go test (TUG).

General pain and function disability were assessed using the Functional Independence Measure (FIM) and the Visual Analogue Scale (VAS). Dyspnea and quality of life were assessed using the medical research chronic (MRC) dyspnea score and the European Quality of Life Scale (EuroQol), respectively.

3. Case Series

3.1. Case 1

P.A.M., a 75-year-old man, was admitted to our RU on 26 July 2021 for PCC following SARS-CoV-2 infection on 23 April 2021, for which he was hospitalized in a COVID hospital with bilateral interstitial pneumonia and acute respiratory failure. Due to worsening respiratory exchanges, he was immediately transferred to the intensive care unit (ICU) and treated with invasive mechanical ventilation. He underwent 6-h ventilation cycles with continuous positive airway pressure (C-PAP) in a prone position every 6 h for the following 2 weeks. Upon admission, he had a few episodes of paroxysmal atrial fibrillation, was treated with pharmacological and electric cardioversions, underwent a percutaneous tracheostomy 2 days after ceasing curarization and beginning weaning from mechanical ventilation, and received single-donor apheresis platelet concentrate transfusions combined with targeted antibiotic therapy following melaena episodes in duodenal angiodysplasia. He was transferred to the pneumology unit of the same hospital on 16 June 2021, and the tracheostomy tube was removed on 6 July 2021. Neurophysiological investigations revealed

moderate sensory-motor distal axonal neuropathy in the upper and lower limbs, with multineuropathic distribution. At admission to our RU, 93 days after the first hospitalization, the nasal-pharyngeal swab result was negative for SARS-CoV-2. The patient was bed-ridden and extremely deconditioned. His body weight was 61.8 kg (pre-hospitalization weight 75 kg) and presented hypokinetic syndrome, paroxysmal atrial fibrillation, post-critical nonthyroidal illness syndrome (low T3 syndrome), arterial hypertension, and prostatic hypertrophy (treated with silodosin 4 mg/day). Moderate malnutrition, according to the GLIM criteria (Cederholm et al., 2019), and probable sarcopenia, as assessed by handgrip strength (16 kg), were present. Hematological biomarkers were in the suboptimal range (Table 1). Subjectively, the patient reported early fatigue and dyspnea after minimal effort and a deflected mood. A color Doppler echocardiogram (GE Medical Systems GE medical, Casoria, Italy; Vivid 7 dimension) revealed normal values and absence of arrhythmias. Therefore, antiarrhythmic and anticoagulation therapy was ceased, maintaining only bisoprolol 1.25 mg/day to avoid bradycardia due to aortic valve insufficiency and adding ramipril 2.5 mg/day to control arterial hypertension. Pantoprazole 20 mg/day as routine treatment was continued throughout the hospitalization.

Table 1. Case 1 admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	61.8	63.2
	Height (cm)	169	169
	BMI (kg/m^2)	21.63	22.12
Hematological Biomarkers	ALT (U/L)	204	14
	AST (U/L)	167	14
	GGT (U/L)	387	91
	CRP (mg/dL)	0.3	0.1
	ESR mg/dL	34	18
Physical Performance	Handgrip strength (kg)	16.6	17.5
	TUG (s)	Bedridden	11.31
	FIM scale	73/126	124/126
	VAS function	90/100	10/100
Pain	VAS pain	30/100	20/100

Individual Rehabilitation Program Timeline

On 27 July 2021, he started physiotherapy and nutritional intervention. WBC started on 15 September 2021, as he was able to stand unsupported for more than 2 min.

Nutritional intervention: The total energy intake was calculated at 30 kcal/die/kg, and protein intake was between 1 and 1.3 g/die/kg of body weight. A 1700 kcal diet was started with a composition of 84 g of protein (1.36 g/kg weight), 52 g of lipids (0.84 g/kg), and 219 g (3.5 g/kg) of carbohydrates. The patient also received oral supplementation through a multivitamin, essential amino acids 5 g (1200 mg l-leucine; 650 mg l-lysine; 625 mg l-isoleucine; 625 mg l-valine; 350 mg l-threonine; 150 mg l-cysteine; 150 mg l-histidine; 100 mg l-phenylalanine; 50 mg l-methionine; 30 mg l-tyrosine; 20 mg l-tryptophan), minerals, and probiotics.

Physiotherapy: The patient started with progressive postural trunk control and passive/assisted exercises for the lower and upper limb muscles to improve proper activation and increase strength. One week later, he succeeded in reaching the standing position and maintaining it for 15 s. The strengthening exercises' intensity for the trunk and lower/upper limbs was progressively increased. Three weeks after admission to our unit, he was able to stand unsupported for 2 min and walk a few steps with a walker. A week later, he also started moderate aerobic training with a cycle ergometer at an intensity of 3.5 METS and for a duration of 5–10 min at a moderate subjective perception of fatigue. The SpO2 value while exercising moderately was 89% and 92% at rest. A few days later, P.A.M. was able to walk with one cane for 20 m; thus, balance training was started. At the end of week 5 of

rehabilitation, he was able to walk without support for more than 100 m, aerobic training volume was increased (intensity 4.5 METS, duration 20–25 min), and SpO2 during exercise reached 97%. At the end of week 6, he walked outdoors for 400 m. The total duration of the rehabilitation stay was nearly 7 weeks.

WBC: Three weeks after admission to our RU, he underwent the first of a total of 15 daily WBC sessions over 4 weeks. No adverse events were recorded. The average reduction in skin temperature recorded was −16.75 °C with a maximum delta value of −19.9 °C between pre-and post-session temperatures. The lowest temperature, recorded at the level of the popliteal fossa, was 14.2 degrees centigrade.

Final assessment: The patient reported subjective improvement in breathing, reduced weakness, reduced functional and general pain, and improved quality of sleep at night. From then on, improvements in subjective fatigue, joint mobility, and muscle strength, as well as SpO2 values during exercise, continued until discharge, nearly 7 weeks after admission. Despite the small weight increase, the patient's inflammatory, metabolic, and nutritional markers substantially improved (Table 1). The reported patient's satisfaction, tolerance, and compliance specifically related to WBC were excellent. He rated WBC as very effective and a very important component of his rehabilitation program.

3.2. Case 2

B.M., a 53-year-old woman, was admitted to our RU for PCC on 17 August 2021 after a SARS-CoV-2 infection on 20 November 2020, for which no hospitalization was needed. In the months following the infection, she experienced persistent generalized fatigue and widespread musculoskeletal pain, hindering her capacity to cope with the full range of activities of daily living. She was eventually referred by her family doctor for a rehabilitation program aimed at restoring her capacities. At admission, her body weight and height were 89.6 kg and 1.64 m, respectively, with a BMI of 33.31 kg/m^2 and a waist circumference of 111 cm. In the last 5 years, she suffered from type 2 diabetes mellitus, which was treated with metformin, and hypertension, which was under pharmacological control. Binge eating and bipolar disorders were also present. At admission, the patient was complaining of low back pain radiating to the left foot, and a reduction in global functioning and independence in daily living activities. She was able to stand and walk independently for short/medium distances, but with the onset of pain and early fatigue. Reduced flexibility limited her ability to kneel, bend forward, and pick up objects from the floor. Body composition as assessed by a body impedance analysis (BIA) was: FM = 44 kg (49.1%); FFM = 45.6 kg (50.9%); and MM = 26.4 kg (29.5%). Hematological biomarkers showed unbalanced lipidic and glucidic profiles (Table 2). Pharmacological therapy consisted of: cholecalciferol 25,000 IU/week, omeprazole 400 mg/day, metformin 1000 mg/day, Triatec 5 mg/day, Empagliflozin 250 mg/day, Resilient 83 mg/day, Pregabalin 75 mg/day, and Felison 15 mg/day.

Table 2. Case 2 admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	89.6	85
	Height (cm)	164	164
	BMI (kg/m^2)	33.31	31.6
	Waist circumference	111	105
	FM (kg; %)	44; 49.1	39.9; 46.3
	FFM (kg; %)	45.6; 50.9	46.3; 53.7
	MM (kg; %)	26.4; 29.5	28; 32.5
	ASMM (kg; %)	17.7	18

Table 2. *Cont.*

		Admission	Discharge
Hematological Biomarkers	ALT (U/L)	22	26
	GGT (U/L)	22	15
	HBA1C (mmol/mL; %)	62; 7.8	54; 7.1
	Glucose (mg/dL)	183	117
	HDL (mg/dL)	41	40
	LDL (mg/dL)	159	83
	Triglycerides (mg/dL)	256	164
Physical Performance	6MWT	495	565
	Handgrip strength (kg)	23.4	23.2
	TUG (s)	8	7.54
	FIM scale	123/126	124/126
	VAS function	28/100	5/100
	VAS pain	22/100	6/100
Pain	VAS pain	22/100	6/100
Trunk Range of Motion	Extension °	10	10
	Flexion °	80	90
	Left lateral bending °	20	25
	Right lateral bending °	20	25

Individual Rehabilitation Program Timeline

On 26 August 2021, she started physiotherapy and nutritional intervention. WBC started on 9 September. The final evaluation of clinical parameters was on 22 September 2021.

Nutritional intervention: The patient was put on a hypocaloric diet of 1450 kcal/day to lose 5–10% of the initial weight. The diet composition was: 75 g/day of protein (21% of total kcal daily intake), 44 g/day of lipids (27%), and 188 g/day (52%) of carbohydrates.

Physiotherapy: Physiotherapy included postural physiotherapy, consisting of several motor control exercises performed while lying, sitting, and standing. The purpose for the patient was to increase thoracic mobility, improve posture, improve lumbar-pelvic muscles' coordination, improve diaphragmatic action, and reduce the respiratory accessory muscles co-contraction. In the first week of physiotherapy, physical activity consisted of decompression techniques while lying down, and progressive proprioceptive exercises while seated were introduced later. After 2 weeks, the program was implemented with progressive body weight exercises using barbells and exercise balls to train the major muscle groups of the lower and upper limbs and core.

WBC: The patient underwent a total of 10 WBC sessions over two weeks. The average reduction in skin temperature recorded was 10.3 ± 5.7 °C degrees with a maximum delta value of 24.3 °C between pre-and post-session temperature. The lowest temperature recorded was 9.2 °C, after the 9th cryostimulation session, at the level of the popliteal fossa. No adverse events were recorded.

Final assessment: The patient showed markedly improved metabolic parameters, physical performance, and strength, and had reduced functional and general pain. In addition, she improved the ability to perform flexion and extension tasks of the trunk (Table 2). Daily functional activities, initially very limited, could be performed smoothly; in fact, she was able to pick up objects from the ground without difficulties. She rated WBC as very effective and a very important component of her rehabilitation program, and her satisfaction specifically related to WBC was excellent.

3.3. Case 3

F.F., a 62-year-old woman, was admitted to our RU on 21 September 2021 for PCC following SARS-CoV-2 infection in November 2020, for which no hospitalization was required. In the months following the acute infection, she experienced persistent dyspnea for

minimal efforts, muscle soreness, and early fatigue, negatively impacting her capacity to perform daily chores and quality of life. The patient also suffered from obstructive sleep apnea syndrome (OSAS), which was treated with C-PAP at night at a pressure of 11 cm H_2O. She presented a history of right humerus osteochondroma, psoriatic arthritis, fibromyalgia, dyslipidemia, and Sjögren's syndrome. At admission in our RU, she was reporting chronic fatigue and oxygen saturation of 97% at rest, but dyspnea (MRC score 4) was already present, even with light efforts such as dressing. A cough and chest pain were absent, but the poor quality of sleep and muscular soreness markedly limited her ability to cope with basic activities of daily living. The patient's body weight was 136.4 kg and body height was 1.82 m, with a BMI of 41.18 kg/m^2 and a waist circumference of 138 cm. The patient's body composition, assessed with a body impedance analysis (BIA), was: FM = 76.9 kg (56.4%); FFM = 59.5 kg; (43.6%); and MM = 33.1 kg (24.3%); a hematological test, depicted in Table 3, showed that several inflammation markers were at a suboptimal level, but a high value of lactate dehydrogenase (LDH) was found. Liver dysfunction markers, and nutritional and metabolic parameters were in a suboptimal range, but an elevated triglycerides value showed an unbalanced lipidic profile. Pharmacological therapy consisted of: pantoprazole 40 mg/day, magnesium and lobivon 5 mg/day, canrenone 50 mg/day, plaquenil 200 mg/day, cardioaspirin 100 mg/day, Arcoxia 90 mg/day, allopurinol 300 mg/day, and Seripnol 1 mg/day.

Table 3. Case 3 admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	136.4	130.8
	Height (cm)	182	182
	BMI (kg/m^2)	41.18	39.49
	Waist circumference	138	127
	FM (kg; %)	76.9; 56.4	74.4; 56.5
	FFM (kg; %)	59.5; 43.6	57.2; 43.5
	MM (kg; %)	33.1; 24.3	31.2; 23.7
	ASMM (kg; %)	27.6	25
Hematological Biomarkers	ALT (U/L)	16	16
	GGT (U/L)	12	11
	HBA1C (mmol/mL; %)	37; 5.5	37; 5.5
	Glucose (mg/dL)	95	98
	HDL (mg/dL)	42	45
	LDL (mg/dL)	114	112
	Triglycerides (mg/dL)	220	179
Physical Performance	Handgrip strength (kg)	15	15.6
	TUG (s)	8	7
	FIM scale	105/126	119/126
	VAS function	50/100	18/100
	EuroQol	50/100	75/100
	MRC dyspnea	4/5	2/5
Pain	VAS Pain	100/100	57/100
Trunk Range of Motion	Extension °	20	20
	Flexion °	60	60
	Left lateral bending °	30	25
	Right lateral bending °	30	30

Individual Rehabilitation Program Timeline

On 21 September 2021, she started physiotherapy and nutritional intervention. WBC started on 23 September 2021. The final evaluation of clinical parameters was on 15 October 2021. Baseline and final assessments are shown in Table 3.

Nutritional intervention: A hypocaloric diet of 1650 kcal/day was started to lose 5–10% of the initial weight. The diet composition was: 75 g/day of protein (18% of total kcal daily intake), 45 g/day of lipids (24%), and 240 g/day (58%) of carbohydrates.

Physiotherapy: The goal was to obtain an improvement in respiratory capacity, tolerance to effort, and independence, and a reduction in general pain. In the first week of physiotherapy, initial physical activity therapy consisted of decompression techniques while lying down, and progressive proprioceptive exercises while seated were introduced later. After 2 weeks, we implemented progressive body weight exercises using barbells and exercise balls to train the major muscle groups of the lower and upper limbs and core. The rehabilitation program also included respiratory physiotherapy, consisting of several motor control exercises performed while lying, sitting, and standing, with the aim of increasing thoracic mobility, improving posture, improving lumbar-pelvic muscles' coordination, improving diaphragmatic action, and reducing the respiratory accessory muscles co-contraction [27].

WBC: The patient underwent a total of 12 WBC sessions over 3 weeks. The average reduction in skin temperature recorded was 13.09 $\pm$ 4.26 °C degrees, with a maximum delta value of 21.5 °C between pre-and post-session temperature, at the level of the popliteal fossa after the 9th treatment (the lowest temperature registered was 12.2 °C). No adverse events occurred.

Final assessment: Despite her weight loss, the patient's metabolic parameters did not vary considerably. On the other hand, she reported noticeable improvements in physical performance and respiratory capacity (Table 3). In fact, dyspnea was absent in all basic activities of daily living, and she was able to walk 20 min without reporting shortness of breath. A moderate perception of fatigue was still present only while walking uphill or climbing stairs. She was very enthusiastic about the WBC protocol, reporting improved quality of sleep and quality of life, and a reduction in functional and general pain and muscle fatigue.

3.4. Case 4

S.R., a 43-year-old woman, was admitted to our RU for PCC following SARS-CoV-2 infection on 5 October 2021. From 22 December 2020 to 3 February 2021, she was hospitalized for secondary interstitial pneumonia in a COVID hospital. Due to worsening of the respiratory exchanges, she was transferred to the ICU and treated with invasive mechanical ventilation. She also suffered a methicillin-resistant Staphylococcus epidermidis infection, which was treated with daptomycin. The patient was bedridden for a total of 35 days. At admission to our RU, her body weight was 116.2 kg, body height 157.5 cm, BMI 46.84 kg/m^2, and waist circumference 129 cm. She had been suffering from hypertension and dyslipidemia for 7 years and had undergone previous surgery for herniated discs in the cervical spine. In addition, she presented latent nocturnal respiratory failure, OSAS which was treated with C-PAP therapy at night (7.6 cm H_2O pressure), daytime sleepiness, and basal hyperinsulinism (HOMA index 11.28), indicative of insulin resistance and steatotic hepatopathy, which was also confirmed by elevated hematological values of ALT 38 U/L. She also had a previous diagnosis of polycystic ovarian syndrome. She was able to perform sit-to-stand at a slow pace, and was able to stand and walk a few steps with support. She was reporting severe dyspnea, muscular and generalized fatigue, severe pain at the lumbar and bilateral shoulder level which made it impossible for her to perform even basic daily activities, a marked deterioration in sleep quality, depression, and anxiety due to a traumatic memory of intensive care. In the last year, the patient had experienced weight-cycling syndrome, with weight oscillations of 10 kg. The patient's body composition, assessed with a body impedance analysis (BIA), was: FM = 60.1 kg (51.7%); FFM = 56.1 kg; (48.3%); MM = 38 kg (32.7%); and ASMM = 23.8. Hematological biomarkers (Table 4) showed an elevated inflammation status and hepatic unbalanced profile. Glycemic and insulinemic values were suggestive of insulin-resistance status. Pharmacological therapy consisted of: olmesartan 20 mg/day; bisoprolol 2.5 mg/day; brimonidine 2 mg/mL twice

a day; slow-release metformin 500 mg/day; doxazosin 4 mg/day; atorvastatin 10 mg/day; and pramipexole 0.18 mg/day.

Table 4. Case 4 admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	116.2	109
	Height (cm)	157.5	157.5
	BMI (kg/m^2)	46.84	43.94
	Waist circumference	129	127
	FM (kg; %)	60.1; 51.7	57.4; 52.6
	FFM (kg; %)	56.1; 48.3	51.7; 47.4
	MM (kg; %)	38; 32.7	32.5; 29.8
	ASMM (kg; %)	23.8	21.4
Hematological Biomarkers	ALT (U/L)	38	32
	AST (U/L)	18	18
	GGT (U/L)	20	14
	HBA1C (mmol/mL; %)	37; 5.5	34; 5.3
	Glucose (mg/dL)	100	88
	Insulin (mU/L)	45.7	17.7
	Total cholesterol (mg/dL)	165	114
	HDL (mg/dL)	42	34
	LDL (mg/dL)	107	63
	Triglycerides (mg/dL)	130	87
	Ferritin (µg/L)	127	139
	CRP (mg/dL)	0.5	0.3
	ESR (mg/dL)	30	17
	LDH (U/L)	235	195
Physical Performance	Handgrip strength (kg)	15.9	7.4
	TUG (s)	9.42	7.40
	FIM scale	114/126	121/126
	VAS function	53/100	40/100
	EuroQol	30/100	50/100
	MRC dyspnea	3/5	2/5
Pain	VAS Pain	53/100	40/100
Trunk Range of Motion	Extension °	20	20
	Flexion °	60	60
	Left lateral bending °	30	25
	Right lateral bending °	30	30

Individual Rehabilitation Program Timeline

On 6 October 2021, she started physiotherapy and nutritional intervention. WBC started on 15 October 2021. The final evaluation of clinical parameters was on 2 November 2021.

Nutritional intervention: A hypocaloric and low carbohydrate diet of 1350 kcal/day was started to lose 5–10% of the initial weight and to improve the borderline glycemic and insulinemic profile (fasting glucose 100 mg/dL; insulin 45.7 mU/L; glycated hemoglobin 37 mmol/mL (5.5%)). The diet composition was: 86 g/day of protein (26% of total kcal daily intake), 40 g/day of lipids (27%), and 167 g/day (47%) of carbohydrates. After discharge from the hospital, the patient was advised to continue with the same diet at home.

Physiotherapy: Initially, physiotherapy consisted of active physical therapy based on body weight exercises. The rehabilitation program also included two daily sessions of moderate aerobic training, postural control exercises, stretching, joint mobility, and body weight strengthening exercises. The patient also underwent antalgic electrotherapy in the lumbar spine and joined respiratory physiotherapy classes.

WBC: She underwent a total of 10 WBC sessions over two weeks and no adverse effects occurred. The average reduction in skin temperature recorded was 10.9 ± 5.7 °C with a maximum delta value of 21.1 °C between pre- and post-session temperature at the

level of the popliteal fossa after the 10th WBC treatment (in this spot and in this session, we also registered the lowest temperature that this patient reached during WBC protocol, equal to 13.2 °C).

Final assessment: The patient reported improved sleep quality, mood, physical performance, and joint range-of-motion, and reduced dyspnea, muscular fatigue, and general pain. Her metabolic and inflammatory parameters improved considerably, as did her body weight and composition (Table 4). The patient was particularly enthusiastic about the WBC protocol. From her perspective, she recognized the important role of this treatment in the beneficial effects she was experiencing, and rated WBC as a very effective component of her rehabilitation program.

3.5. Case 5

B.G., a 62-year-old woman, was hospitalized in November 2020 with respiratory failure and bilateral interstitial pneumonia due to SARS-CoV-2 infection. During her acute hospitalization, she underwent 6-h C-PAP ventilation cycles, day and night, for 2 weeks and was discharged after 15 days, with indication to continue C-PAP treatment at home only during night hours. She was admitted to our RU on 13 December 2021. At admission, she was reporting PCC, consisting of daytime sleepiness and asthenia, chronic fatigue and dyspnea at minimal effort, deterioration in sleep quality, and depression. The patient's body weight and height were 88.5 kg and 150 cm, respectively, with a BMI of 39.33 kg/m^2 and a waist circumference of 110 cm. The patient's body composition, assessed with a BIA, was: FM = 45.6 kg; (51.5 %); FFM = 42.9 kg; (48.5%); and MM = 20.9 kg (23.6%). The patient's medical history revealed that she had type 2 diabetes mellitus, severe obesity, hypertension under pharmacological control, an eating disorder, depression treated with fluoxetine, sequelae of L5-S1 stabilization surgery, and obstructive sleep apnea syndrome treated with BiPAP therapy. Given the absence of contraindications, we proposed the patient complete a cycle of WBC. Hematological biomarkers showed elevated values of the main inflammation markers on admission; liver dysfunction markers and nutritional and metabolic parameters were indeed in a suboptimal range (Table 5). Pharmacological therapy was: telmisartan 40 mg/day; tapentadol 25 mg/day; pantoprazole 40 mg/day; nebivolol 5 mg/day; furosemide 25 mg/day; metformin 500 mg/day; fluoxetine 20 mg/day; atorvastatin 10 mg/day; pramipexole 0.18 mg/day; and dulaglutide 1.5 mg/day.

Table 5. Case 5 Admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	88.5	85.4
	Height (cm)	150	150
	BMI (kg/m^2)	39.33	37.96
	Waist circumference	110	110
	FM (kg; %)	45.6; 51.5	39.7; 46.2
	FFM (kg; %)	42.9; 48.5	46.3; 53.8
	MM (kg; %)	20.9; 23.6	28.5; 33.1
	ASMM (kg; %)	22.3	17.6
Hematological Biomarkers	ALT (U/L)	14	8
	AST (U/L)	13	11
	GGT (U/L)	16	13
	HBA1C (mmol/mL; %)	39; 5.7	35; 5.4
	Glucose (mg/dL)	80	82
	Insulin (mU/L)	13	18.9
	Total cholesterol (mg/dL)	170	131
	HDL (mg/dL)	49	42
	LDL (mg/dL)	103	76
	Triglycerides (mg/dL)	141	94
	Ferritin (µg/L)	35	41
	CRP (mg/dL)	0.9	0.7

Table 5. *Cont.*

		Admission	Discharge
	ESR (mg/dL)	56	35
	LDH (U/L)	178	159
	D-dimer (µg/L)	798	478
	Fibrinogen (mg/dL)	453	340
Physical Performance	Handgrip strength (kg)	16.6	16.2
	TUG (s)	10.5	8.7
	FIM scale	124/126	124/126
	VAS function	49/100	29/100
	EuroQol	60/100	80/100
	MRC dyspnea	3/5	2/5
Pain	Vas pain	50/100	28/100
Trunk Range of Motion	Extension °	10	15
	Flexion °	50	80
	Left lateral bending °	15	15
	Right lateral bending °	15	15

Individual Rehabilitation Program Timeline

On 14 December 2021, she started physiotherapy and nutritional intervention. WBC started on 16 December 2021. The final evaluation of clinical parameters was on 10 January 2022.

Nutritional intervention: A hypocaloric diet of 1350 kcal/day was started in order to lose 5–10% of the initial weight and to improve glyco-metabolic compensation. The diet composition was: 66 g/day of protein (19% of total kcal daily intake), 43 g/day of lipids (29%), and 176 g/day (52%) of carbohydrates, and, after discharge from the hospital, the patient was advised to continue with the same diet also at home.

Physiotherapy: The physiotherapist reported several physical therapy sessions were missed because the patient was reporting excessive fatigue and sleepiness during the day. The physical exercise program was therefore inconsistent. Progressive body weight exercises were carried out to strengthen the lower limbs and the spinal muscles. We proposed WBC as an alternative treatment to exercise since this treatment requires less drive, motivation, and active involvement in physical effort.

WBC: The patient underwent a total of 10 WBC sessions over two weeks. The average reduction in skin temperature recorded was 10.7 ± 5.7 °C degrees with a maximum delta value of 20.4 °C between pre-and post-session temperature. The lowest temperature recorded was 12.0 °C after the 4th cryostimulation session at the level of the quadriceps. No adverse events were recorded.

Final assessment: Despite initial non-optimal compliance, we registered an improvement in the patient's compliance to the rehabilitation program after the implementation of WBC. At the end of the rehabilitation program, the patient reported a higher quality of life, with marked improvement in physical performance and trunk range-of-motion, and reduced dyspnea and general pain. Most of the metabolic parameters and inflammatory biomarkers decreased considerably, as did body weight (Table 5). The patient's satisfaction and compliance to the WBC protocol were excellent, and she recognized that WBC implementation was a turning point in her rehabilitation program.

3.6. Case 6

C.B., a 48-year-old man, suffered from a SARS-CoV-2 infection in March 2020. Due to the worsening of clinical conditions and respiratory capacity, he was admitted to the ICU where he was intubated and mechanically ventilated. He was hospitalized there for 15 days and discharged after a negative swab. He was then bedridden for about 2 months. During the SARS-CoV-2 infection he also developed type 2 diabetes mellitus. He was admitted

to our RU on 7 January 2022. At admission, his body weight and height were 140 kg and 189 cm, respectively, with a BMI of 39.19 kg/m^2; thus, presenting a severe obesity condition. He also presented with chronic low back pain, medial knee pain, and OSAS, which was treated with C-PAP and oxygen therapy (2 L/min). He was experiencing dyspnea from the slightest effort, persistent asthenia, generalized fatigue, low tolerance to effort, poor quality of sleep, retrograde amnesia, and anomia. Polysomnography revealed 90 apneas per night. The patient was also reporting deterioration of mood and sleep, daytime sleepiness, and difficulty in performing basic daily activities, especially in the morning hours. The patient's body composition, assessed with a body impedance analysis (BIA), was: FM = 65.4 kg (47.3%); FFM = 72.9 kg; (52.7%); MM = 50.4 kg (36.4%); and ASMM 30.7 kg. The patient was admitted to undergo a metabolic, nutritional, motor, and respiratory rehabilitation program. Hematological biomarkers showed elevated values of the main inflammation markers. Liver dysfunction markers and the lipidic profile were in a normal range. The glucidic profile was compatible with the diagnosis of DMT2. Pharmacological therapy consisted of metformin 500 mg/day.

Individual Rehabilitation Program Timeline

On 10 January 2022, he started physiotherapy and nutritional intervention. WBC started on 13 January 2022. The final evaluation of clinical parameters was on 2 February 2022.

Nutritional intervention: A hypocaloric diet of 1800 kcal/day was started in order to lose 5–10% of the initial weight and to improve glyco-metabolic compensation. The diet composition was: 94.3 g/day of protein (20% of total kcal daily intake), 50.7 g/day of lipids (25%), and 255 g/day (55%) of carbohydrates, and, after discharge from the hospital, the patient was advised to continue with the same diet also at home.

Physiotherapy: The patient was reporting daily asthenia and dyspnea with minimal effort. Overall, the patient was showing the ability to cope with basic daily activities, but with pain in the lower back and in the lower limbs. During the first week, the physiotherapy sessions consisted of manual therapy and 20 min of body weight exercise with prolonged recovery times. In weeks two and three, he continued body weight muscle strengthening exercises, with the secondary aim of learning exercises to be performed independently at home after discharge. Initially, it was aimed at the correct execution of the movement, with recovery times dilated to avoid overexertion. In week three, recovery times shortened considerably. During the last week, we increased the number of repetitions and the total volume of exercise, stimulating the patient's motivation for continuing home-based exercise after discharge.

WBC: The patient underwent a total of 10 WBC sessions in two weeks. Starting from the fourth session, beneficial effects from the treatment with WBC were reported and no adverse effects were recorded. He then started to undergo the WBC treatments without a T-shirt, and, consequently, reported greater positive effects. The average reduction in skin temperature recorded was 10.5 $\pm$ 3.5 °C with a maximum delta value of 17.2 °C between pre-and post-session temperature after the 6th WBC session at the level of the calf (the temperature was 14.2 °C, the lowest reached by this patient).

Final assessment: At the end of the rehabilitation program, the patient reported a higher quality of life and an improvement in physical performance with reduced dyspnea and general pain. Most of the metabolic parameters, especially glucose, HBA1C, and the inflammatory biomarker CRP, decreased considerably, as did the body weight and composition (Table 6). The patient rated WBC as a very effective and beneficial component of his rehabilitation program.

Table 6. Case 6 admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	140	134.8
	Height (cm)	189	189
	BMI (kg/m^2)	39.19	37.74
	Waist circumference	129	126
	FM (kg; %)	65.4; 47.3	60.7; 44.7
	FFM (kg; %)	72.9; 52.7	75.1; 55.3
	MM (kg; %)	50.4; 36.4	44.4; 75.1
	ASMM (kg; %)	30.7	30.6
Hematological Biomarkers	ALT (U/L)	51	70
	AST (U/L)	31	44
	GGT (U/L)	26	20
	HBA1C (mmol/mL; %)	50; 6.7	44; 6.2
	Glucose (mg/dL)	151	117
	Total cholesterol (mg/dL)	192	182
	HDL (mg/dL)	48	39
	LDL (mg/dL)	122	122
	Triglycerides (mg/dL)	174	134
	Ferritin (µg/L)	639	531
	CRP (mg/dL)	1.1	0.1
	ESR (mg/dL)	20	13
	LDH (U/L)	216	193
	D-dimer (µg/L)	514	435
Physical Performance	6MWT (m)	510	568
	Handgrip strength (kg)	49.8	49.3
	VAS function	25/100	3/100
	EuroQol	70/100	90/100
	MRC dyspnea	1/5	0/5

3.7. Case 7

M.M., a 61-year-old woman, suffered a SARS-CoV-2 infection in March 2021, after which she was bedridden at home (from 23 March to 11 April) and not hospitalized. She was diagnosed with bilateral interstitial pneumonia secondary to the infection, which was treated for 16 days with deltacortene 150 g/day, amoxicillin 875 mg/twice daily, and paracetamol 500 mg/day. After the acute phase, she experienced chronic fatigue and cough, muscle pain, strong anxiety, reduced salivation, low exercise tolerance, and dyspnea at the slightest effort. The patient complained of significant hand pain due to rheumatoid arthritis, and cervical spine and dorsal spine pain. She also reported shortness of breath and sleep apnea and, in parallel, reduced sleep and quality of life. These symptoms, which were not present before the COVID-19 infection, persisted until the date of admission to our RU (18 January 2022). Since no contraindications were present, we proposed treatment with WBC. The patient's medical history revealed severe obesity, OSAS, mixed dyslipidemia, serum-negative rheumatoid arthritis, non-autoimmune hypothyroidism for about 30 years, and hypertension under good pharmacological control. She also presented altered fasting blood glucose levels and impaired glucose tolerance, generalized anxiety disorder, and an eating disorder. Inflammation and liver dysfunction markers were in a normal range, whereas nutritional and metabolic parameters confirmed a picture of dyslipidemia and an unbalanced glycemic and insulinemic profile (Table 7). Pharmacological therapy was Eutirox 0.1 mg/day; Almarytm 100 mg/day; olmesartan 40 mg/day; Folin 5 mg/day; atorvastatin 10 mg/day; tocilizumab 162 mg/day; Reumaflex 12.5 mg/day.

Table 7. Case 7 admission and discharge parameters.

		Admission	Discharge
Anthropometry and Body Composition	Weight (kg)	111.4	108.1
	Height (cm)	168	168
	BMI (kg/m^2)	39.47	38.3
	Waist circumference	136	124
	FM (kg; %)	57.3; 34.1	55.5; 51.2
	FFM (kg; %)	52.0; 31.0	52.9; 48.8
	MM (kg; %)	29.8; 27.3	29.3; 27
	ASMM (kg; %)	21.1	22.0
Hematological Biomarkers	ALT (U/L)	30	41
	AST (U/L)	19	24
	GGT (U/L)	21	17
	HBA1C (mmol/mL; %)	40; 5.8	40;5.8
	Glucose (mg/dL)	117	99
	Insulin (mU/L)	33.2	24.1
	Total cholesterol (mg/dL)	271	124
	HDL (mg/dL)	56	46
	LDL (mg/dL)	180	62
	Triglycerides (mg/dL)	141	87
	CRP (mg/dL)	0.0	0.0
	ESR (mg/dL)	13	2
Physical Performance	TUG (s)	6.54	10.18
	FIM	123/126	124/126
	VAS function	65/100	0/100
	EuroQol	57/100	60/100
	MRC dyspnea	1/5	0/5
Pain	VAS pain	48/100	30/100

Individual Rehabilitation Program Timeline

On 18 January 2022, she started physiotherapy and nutritional intervention. WBC started on 21 January 2022. The final evaluation of clinical parameters was 3 February 2022.

Nutritional intervention: A hypocaloric diet of 1500 kcal/day was started in order to lose 5–10% of the initial weight and to improve the glyco-metabolic status. The diet composition was: 70 g/day of protein (18% of total kcal daily intake), 47.3 g/day of lipids (27%), and 207 g/day (55%) of carbohydrates.

Physiotherapy: The goal was to obtain weight loss, optimization of ventilotherapy, improvement in quality of life, muscle function, and strength, and reduction in fatigue-related symptoms secondary to Long COVID. The patient underwent a physiotherapy program with specific techniques (SMARTERehab) [27] aimed at improving posture and motor control, intra-abdominal pressure, rib cage mobility, and correct muscle activation and coordination. During the first week, the patient was treated in the lying position with manual treatments and then began to perform postural transitions from lying to sitting. In the second week, anti-gravity exercises were introduced for both upper and lower limbs with prolonged recovery periods between exercise bouts. The intensity of the physiotherapy activity was modulated daily according to the reported perception of fatigue and pain. At discharge, the patient reported a reduction in left knee pain, but persisting pain in the hands and cervical spine, and dyspnea, now occurring at medium to heavy exertions. On February 2, the patient had an episode of subacute back pain, which affected final evaluation scores.

WBC: The patient underwent a total of 10 WBC sessions in 3 weeks. The average reduction in skin temperature recorded was 10.5 $\pm$ 6.4 °C degrees, with a maximum delta value of 18.9 °C between pre- and post-session temperature, at the level of the popliteal fossa after the first treatment (the lowest temperature registered was 10.3 °C). She was very compliant and enthusiastic about the WBC protocol, reporting several beneficial

effects such as reduction in chronic pain and dyspnea, reduction in breathing difficulties, improvement in quality of sleep, and fatigue reduction. The patient's compliance and satisfaction with the WBC protocol were excellent. No adverse effects occurred.

Final assessment: The patient improved in most of the metabolic and body composition parameters. The patient reported a higher quality of life, showing a marked improvement in most of the physical performance tests and general pain (Table 7). A sudden lumbar spine pain negatively affected the final TUG test result.

4. Summary of Results

This case series investigated longitudinal changes in physical and cognitive functioning in seven patients with PCC after treatment with WBC. The purpose of this report was to clarify the possible adjuvant role of WBC in rehabilitation programs for PCC patients. The PCC cases we reported were heterogeneous and showed different degrees of severity. All patients reported clinically significant improvements related to health and functioning. The most noticeable improvements were observed in those patients who had a lower functional status on admission. In addition, for all reported cases, it was observed that the introduction of the WBC sessions represented a turning point in the patient's subjective and objective parameters. Patients reported after a couple of WBC sessions "further improvements" that they felt were related to the implementation of this treatment in their rehabilitation programs. The most frequently reported benefits after the WBC protocol were improved quality of life, sleep, and mood, and reduced fatigue, dyspnea, and pain. Anthropometric measures and body composition parameters improved in each case, as did their physical performance. We also recorded a reduction in key markers of hematological inflammation, confirming the anti-inflammatory action of WBC. Interestingly, cryostimulation was well tolerated by all patients who enthusiastically adhered to the WBC sessions.

5. Discussion

A surprising number of extra-pulmonary manifestations of severe acute respiratory SARS-CoV-2 infection have been described with a review of imaging [28], shedding some light on a range of musculoskeletal, nerve, joint, and bone involvement, and leading to the manifestation of prolonged symptoms. However, the rationale for prescribing WBC in post-COVID symptoms appears in line with the existing evidence of clinical and functional benefits following WBC documented in other musculoskeletal, neurological, and psychiatric conditions. Pain, fatigue, and alleviation of inflammatory symptoms after WBC, as also shown in this report, appear to be related to reduced nerve conduction and acetylcholine formation and lower levels of oxidative stress and inflammation [29], but a full understanding of the underlying mechanisms is yet to be fully disclosed. Importantly, the benefits of WBC seem to appear rapidly (1 week). WBC seems to trigger rapid anti-inflammatory actions, which could explain our encouraging results and support its use as a booster for rehabilitation programs, as the improvement in physical performance in each case described was noteworthy. In support of this suggestion, findings by Lubkowska and collaborators [29] highlighted that WBC leads to a rapid decrease in the concentration of the pro-inflammatory cytokines interleukin 1a (IL-1a), and a rapid increase in the anti-inflammatory cytokines interleukin 10 (IL-10). In addition, the use of cryostimulation prior to training or competition has been shown to exert beneficial effects through a multifactorial hypothesis, such as hormonal changes, peripheral vasoconstriction with improved muscle oxygenation, reduced fatigue and pain, an anti-inflammatory effect, and subsequent psychological well-being [30]. Given these known rapid effects, we performed the WBC session early in the day with the goal of improving patients' overall physical performance and improving patients' adherence and motivation to rehabilitation. In conclusion, considering the current severity and prevalence of PCC in the general population, the identification of adjuvants that can act as a booster for rehabilitation programs appears to be of paramount importance. Independent research must proceed with caution in gathering data and evidence from larger studies on the benefits of WBC to avoid dangerous scientific

shortcuts. We are aware of commercial and non-medical use of cryostimulation as some sort of panacea, but scientific evidence of its clinical utility in several specific conditions is growing rapidly.

6. Limitations

Because we provided a variety of interventions, including nutritional and psychological support along with physical exercise, we could not determine to what extent WBC may per se have accounted for observed clinical and functional improvements, and randomized control trials with sham WBC sessions are needed for that purpose. Moreover, the reduction in the inflammatory status we encountered cannot be attributed merely to WBC treatment. In fact, it is known that weight loss results in a reduction in pro-inflammatory markers, suggesting that the anti-inflammatory effect could be a synergic result of WBC and weight loss interventions [31]. Another present limitation of this report, and, in general, in current WBC studies, is that no blinding of participants has been used, which could have influenced the outcomes. However, given the evidence of effectiveness of WBC on a range of symptoms common in PCC, we believe that this case series, written according to the CARE checklist, provides some inputs to promote further research on the use of WBC in boosting the recovery from PCC within a multidisciplinary rehabilitation program. Sturdy evidence that WBC has beneficial effects in various musculoskeletal and neurological conditions indeed exists, but larger and controlled studies on PCC patients are needed to generalize our preliminary suggestions.

Author Contributions: P.C. is the study's principal investigator. Study concept and design were contributed to by P.P., M.G., J.M.F., S.C., M.M. and P.C.; P.P. and M.G. treated the patients with WBC and extracted all necessary data. S.C. analyzed the hematological markers. P.P. wrote the first draft of the manuscript. All authors revised and/or commented on drafts. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Patients were given full information about the scope and the methodology of the study, which was conducted according to the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of Istituto Auxologico Italiano (approval code #2021_05_18_14). Written informed consent was obtained from all experimental patients.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The dataset is available on request.

Conflicts of Interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

Abbreviations and Symbols

ALT: alanine aminotransferase; ASMM: appendicular skeletal muscle mass; AST: aspartate aminotransferase; BIA: body impedance analysis; BMI: body mass index; CIM: critical illness myopathy; C-PAP: continuous positive airway pressure; CRP: C-reactive protein; °: degrees; DMT2: diabetes mellitus type 2.

ESR: erythrocyte sedimentation rate; EuroQol: European Quality of Life Scale; FFM: free fat mass; FIM: Functional Independence Measure; FM: fat mass; GGT: gamma-glutamyl transpeptidase; HBA1C: hemoglobin A1; HDL: high-density lipoprotein; ICU: intensive care unit LDH: lactate dehydrogenase; LDL: low-density lipoprotein; METS: metabolic equivalent of task; MM: muscular mass; OSAS: obstructive sleep apnea syndrome; PCC: post-COVID condition; QoL: quality of life; TUG: Timed Up and Go; VAS: Visual Analogue Scale; 6MWT: 6-min walk test; WBC: whole-body cryostimulation.

Appendix A. Main Contraindications for the WBC Treatment

Chronic wasting disease and hypothermia; asthma; cold allergies; abuse of medications (particularly neuroleptics) and alcohol; abrasion injuries; purulent-gangrenous skin lesions; neuropathies of the sympathetic nervous system; current steroid therapy cycle; current immunoglobulin cycle; cycle with monoclonal antibodies (Rituximab) in progress; inability to maintain prolonged independent standing; claustrophobia; chronic venous insufficiency; arterial hypertension not controlled by current therapy; unstable angina pectoris; peripheral arterial disease; deep vein thrombosis; acute febrile respiratory illness; acute urinary and renal disease; advanced anemia; epilepsy; skin diseases not controlled by current therapy; neoplastic diseases in active phase; active bacterial and viral infections; cardiac diseases such as heart rhythm disorders, valvulopathy, ischemic heart disease; Raynaud's syndrome; pregnancy (from the fourth month); thyroid disease not controlled by current therapy; pace-maker patients; psychiatric disorders not controlled by current therapy.

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