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Original article

Fatigue in Covid-19 survivors: The potential impact of a nutritional supplement on muscle strength and function



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SUMMARY

Background: Fatigue with reduced tolerance to exercise is a common persistent long-lasting feature amongst COVID-19 survivors. The assessment of muscle function in this category of patients is often neglected.

Aim: To evaluate the potential impact of a daily supplementation based on amino acids, minerals, vitamins, and plant extracts (Apportal®) on muscle function, body composition, laboratory parameters and self-rated health in a small group of COVID-19 survivors affected by fatigue.

Methods: Thirty participants were enrolled among patients affected by physical fatigue during or after acute COVID-19 and admitted to the post-COVID-19 outpatient service at Fondazione Policlinico Gemelli in Rome between 1st March 2021 and 30th April 2021. All participants were evaluated at first visit (t0) and at control visit (t1), after taking a daily sachet of Apportal® for 28 days. Muscle function was analyzed using hand grip strength test, exhaustion strength time and the number of repetitions at one-minute chair stand test. Body composition was assessed with bioelectrical impedance analysis (BIA). Laboratory parameters, including standard blood biochemistry and ferritin levels, were evaluated at the first visit and during the control visit. A quick evaluation of self-rated health, before COVID-19, at t0 and t1, was obtained through a visual analogue scale (VAS).

Results: Participants aged 60 years and older were 13 (43%). Females represented the 70% of the study sample. Participants hospitalized for COVID-19 with low-flow oxygen supplementation represented the 43.3% of the study sample while 3.3% received noninvasive ventilation (NIV) or invasive ventilation. Hand grip strength improved from 26.3 Kg to 28.9 Kg ($p < 0.05$) at t1 as compared to t0. The mean time of strength exhaustion increased from 31.7 s (sec) at t0 to 47.5 s at t1 ($p < 0.05$). Participants performed a higher number of repetitions (28.3 vs. 22.0; $p < 0.05$) during the one-minute chair stand test at t1 as compared to t0. A trend, although not significant, in reduction of ferritin levels was found after nutritional supplementation (94.4 vs. 84.3, respectively; $p = 0.01$). The self-rated health status increased by at least 13 points (t0, mean 57.6 ± 5.86 ; t1, mean 71.4 ± 6.73 ; $p < 0.05$).

Conclusions: After 28 days of nutritional supplementation with Apportal® in COVID-19 survivors affected by fatigue with reduced tolerance to exercise, we found a significant improvement in means of muscle strength and physical performance, associated with enhancement of self-rated health status between t0 and t1.

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1. Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) is characterized by several symptoms, with a prevalent pulmonary tropism, especially during the acute phase [1]. Recovery after Sars-CoV-2 infection is heterogeneous amongst individuals, with some

returning to a baseline health status after viral clearance while other displaying persistent long-lasting symptoms [2]. This latter clinical condition is defined as “post Covid-19 syndrome” or Long Covid [3].

Sanitary implications of the Sars-CoV-2 pandemic involved not only those affected by COVID-19, but whoever suffered from mandatory lockdown restrictions [4]. Lifestyle habits of millions of people, including physical activity levels and dietary habits, have drastically changed during the pandemic [4–7]. Social distance and the limitation of usual activities, associated with the fear of contagion, have influenced people’s psychological wellbeing [8]. Particularly, perception of a safe working environment was a crucial aspect for the mental health of those that continued to work throughout the pandemic, including healthcare workers [9].

Fatigue represents one of the most relevant symptoms of Long Covid [2,10]. According to Lombardo et al., fatigue is present in the 60% of COVID-19 survivors aged 50 years and more, but it may also afflict one third of people in the young ages [11]. Extreme weakness affects both people who were hospitalized during the acute phase of COVID-19 and those home-managed [12]. Whether physical fatigue in Long Covid is associated with the decline of muscle function is uncertain. Generally, muscle fatigue is characterized by the decline in the power capacity of muscle [13] and is associated to altered functional performance tests [14]. The majority of people who have been hospitalized for COVID-19 are at high risk of sarcopenia [15], especially in the case of the intensive care units (ICUs) prolonged admission. Notably, the prevalence of malnutrition in hospitalized patients for COVID-19 may reach the 50% [16]. The loss of skeletal mass can last for several months after COVID-19 [17] and may induce a slow and prolonged recovery after the acute illness. However, the assessment of muscle strength and function in this category of patients is often neglected. Individuals with reduced muscle strength or physical performance in comparison to their target population [18], are at higher risk of several negative outcomes [19–23]. In particular, a sub-standard hand grip strength score is a predictor of all-causes mortality [24]. Indeed, prior condition of sarcopenia is associated with more severe COVID-19 and higher risk of its related mortality [25].

Dietary modifications that promote increased daily protein intake may have a pivotal role in the improvement of muscle function [26]. Supplementation with amino acids, such as arginine, seems to act against muscle deterioration, improving anabolism and muscle strength [27]. Furthermore, several studies have also suggested that minerals’ supplementation may promote muscle strength and physical performance [28,29]; among minerals, magnesium seems to reduce inflammatory cytokines and avoid the loss of skeletal mass [30,31]. Moreover, a recent trial has shown that a daily nutritional supplement intake based on amino acids, minerals, vitamins, and plant extracts (Apportal®, Pharmanutra Spa) may improve fatigue amongst Long Covid patients [32].

We performed an exploratory study with the aim of evaluating the impact of a daily supplementation of Apportal® on muscle strength and physical performance, in a small group of COVID-19 survivors affected by fatigue with reduced tolerance to exercise during the acute phase of COVID-19 and/or in the post-acute phase. The secondary aim was to assess if the nutritional supplementation could ameliorate body composition and laboratory parameters. Finally, we aimed to evaluate the impact of the supplementation on self-rated health status on the study population.

2. Materials and methods

The Gemelli Against COVID-19 Post-Acute Care (GAC19-PAC) project is an ongoing initiative developed by the Department of Geriatrics and Orthopedics of the Università Cattolica del Sacro Cuore (Rome, Italy) to investigate long-term consequences of

COVID-19 and their impact on overall health, physical and cognitive performance, and quality of life. From April 2020, the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (Rome, Italy) has established a post-acute outpatient service for people who recovered from COVID-19, called “Day Hospital post COVID-19” [33].

2.1. Study sample

The study population included patients still suffering of long-term sequelae from COVID-19 and admitted to the post-COVID-19 outpatient service between 1st March 2021 and 30th April 2021 [10,33]. Among all admitted patients, physicians selected subjects that reported fatigue associated to reduced tolerance to exercise during the acute phase of COVID-19 and/or in the post-acute phase. Participants were evaluated upon admission to our outpatient service (t0 = first visit) and 28 days later (t1 = control visit). During the time between first and control visit, participants with self-reported fatigue were suggested to take a daily sachet of Apportal®. Patients included in the final evaluation were aged 18 years and older; had an average days that ranged from 30 to 90 days from COVID-19 diagnosis to admission to the outpatient service. We excluded from final analysis those who presented active cancer or recent history of cancer (<5 years), an history of autoimmune diseases, a persistent requirement of oxygen supplementation therapy and the presence of fatigue prior to COVID-19 or worsening of prior fatigue after COVID-19.

Apportal® is a nutritional supplement that contains 19 nutrients including amino acids such as arginine and carnitine, minerals in Sucrosomial® forms such as iron, magnesium, zinc and selenium, group B vitamins, and plant extracts including *Panax ginseng* and *Eleutherococcus senticosus*. Apportal® is commercialized as a single package containing 14 sachets of daily nutritional supplement.

2.2. Data collection

During the first visit (t0), patients were evaluated by a standard comprehensive medical assessment grand to all individuals admitted to our post-acute COVID-19 service [33]. This included medical history before, during and after COVID-19, current medications, long-term self-reported symptoms after COVID-19 [10]. Acute illness severity was categorized as follows: (a) no hospitalization; (b) hospitalization with low-flow oxygen supplementation; (c) hospitalization with noninvasive ventilation (NIV) or intensive care unit (ICU) admission with invasive ventilation. Regular participation in physical activity was defined as the engagement in leisure-time physical activity at the time of the evaluation for a minimum of 120 min per week. Patients who referred self-reported fatigue, were suggested to take a daily sachets of Apportal®. After 28 days of daily supplementation (t1), participants were evaluated at our post-COVID 19 service for a control visit. Long-term self-reported symptoms after COVID-19 and compliance to the suggested supplement therapy were addressed. At both t1 and t0 assessment of muscle strength and physical performance measures, body composition measures, bloods biochemistry measures and self-rated health measure was carried out. Data collection and instrumental measurements were performed by physicians and nurses of the clinic.

2.3. Assessment of muscle strength and physical performance

Muscle strength was measured by handgrip strength using a North Coast hand-held hydraulic dynamometer (North Coast Medical, Inc, Morgan Hill, CA) [34]. The participant was seated on a chair with shoulder in a neutral position, the elbow near the trunk and flexed at 90°, and the wrist in a neutral position (thumbs up) [34].

After one familiarization trial, upper extremity muscle strength was assessed in both hands and the highest value (kg) was used for the analysis. To evaluate muscle resistance, handgrip exhaustion time was calculated after an additional trial, in which participants were asked to maintain the grip and the value was measured in seconds (sec) when strength drops to 50% of its maximum level. Physical performance was evaluated by the one-min sit-to-stand test (1STST). This test is used to primarily evaluate pulse oxygen saturation and potential exercise-induced pulse oxygen desaturation [35], but also muscle capacity [36]. The 1STST test seems to be a reliable tool to evaluate the physical capacity and exertional desaturation after discharge in those who have been hospitalized for COVID-19 [37]. Considering that the 1STST test presents similarities to the timed-up-and-go test (TUG), it represents a valid proxy to assess sarcopenia in line with the TUG as suggested by the European Consensus on Sarcopenia [18]. For the 1STST, participants were asked to stand up from a chair and sit down with their arms folded across the chest for one minute as quickly as possible. A standard armless chair (43–47 cm in height) was used. The back of the chair was stabilized against a wall to ensure safety and stability. The number of times the patient completed the sit-to-stand movements was recorded; higher number reflect better performance [36]. Handgrip strength test, the time of handgrip exhaustion, and the one-min sit-to-stand test (1STST) were evaluated at t0 and t1.

2.4. Assessment of body composition

Body weight was measured through an analog medical scale at t0. Body height was measured using a standard stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Body composition was evaluated through a InBody S10 Bioelectrical Impedance Analyzer (BIA) (Caresmed Srl, Milano, Italy). Considering that this instrument is widely available and portable, BIA represents one of the validated methods to quantify muscle mass [18]. Skeletal muscle mass (SMM) was measured in Kg; body fat mass (BFM) was detected in kg; basal metabolic rate (BMR) was calculated in Kcal; skeletal mass index (SMI) was detected as kg/m² (kg/height in square meters); phase angle was detected in grade.

2.5. Standard blood biochemistry

Blood samples were collected at t0 and t1 by venipuncture after overnight fasting. Hemoglobin was measured in grams per deciliter (g/dL), ferritin in nanograms per milliliter (ng/mL), iron in gamma per deciliter (gamma/dL), serum creatinine in milligrams per liter (mg/L), plasma albumin in grams per liter (g/L), liver enzymes ALT (GPT) in U_i per liter (U_i/L), C-reactive protein in milligrams per liter (mg/L). All laboratory parameters were assessed using standard biochemistry methods on fully automated testing systems. Ferritin represents an inflammatory marker, that reflects the rate of cell damage [38]. Both high ferritin levels and low hemoglobin levels have been found present in patients with severe COVID-19 [39]. High C-reactive protein levels have also been associated to worse outcomes of COVID-19 [40]. Low plasma albumin levels are independently associated with decreased muscle strength [41].

2.6. Self-rated health

A visual analogue scale (VAS) was used to obtain a quick evaluation of self-rated health before COVID-19, at the time of evaluation (t0), and after 28 days of daily supplementation (t1). The VAS is based on a scale from 0 to 100, with 0 corresponding to the worst imaginable health and 100 indicating the best imaginable health [42].

2.7. Statistical analyses

Descriptive statistics were used to describe demographic and key clinical characteristics of the study populations: overall and according to age groups (age ≥ 60 years old, age < 60 years old). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies by absolute value and percentages (%). Repeated Measure T-Test (Paired T-Test) was used to compare differences in means between muscle strength and physical performance measures, body composition measures, bloods biochemistry measures and self-rated health measure. Statistical analyses was carried out by a physician part of the post-COVID outpatient service team.

All data were collected using REDCap, a software that enables a structured electronic data collection. Statistical analyses were performed using R statistical environment (version 4.0).

3. Results

Between the 1st March 2021 and the 30th April 2021, we selected 30 participants among patients admitted to the post-COVID-19 outpatient service [32]. Descriptive statistics of the main characteristics of the study population according to age groups are summarized in Table 1. The majority of participants (17 of 30) were younger than 60 years old. The mean age of the over 60 subgroup was 68.4 (±6.3), while in the under 60 subgroup was 46.7 (±10.08). Females represented the 70% of the study sample (21 females, 9 males). Thirteen patients were hospitalized for COVID-19 and one patient had reported ICU admission (43.3% hospitalized with low-flow oxygen supplementation vs. 3.3% who received

Table 1
Baseline characteristics of the study population according to age.

	Over 60 (N = 13)	Under 60 (N = 17)	Total (N = 30)
Sex			
Male	7 (53.8%)	2 (11.8%)	9 (30.0%)
Female	6 (46.2%)	15 (88.2%)	21 (70.0%)
BMI (Kg/m²)			
Mean (SD)	23.4 (2.50)	23.4 (2.94)	23.4 (2.71)
Median [Min, Max]	23.2 [20.0, 28.4]	23.5 [18.4, 28.7]	23.4 [18.4, 28.7]
Hypertension			
Present	6 (46.2%)	2 (11.8%)	8 (26.7%)
Absent	7 (53.8%)	15 (88.2%)	22 (73.3%)
Heart diseases			
Present	3 (23.1%)	0 (0%)	3 (10.0%)
Absent	10 (76.9%)	17 (100%)	27 (90.0%)
Pulmonary diseases			
Present	4 (30.8%)	2 (11.8%)	6 (20.0%)
Absent	9 (69.2%)	15 (88.2%)	24 (80.0%)
Diabetes			
Present	1 (7.7%)	1 (5.9%)	2 (6.7%)
Absent	12 (92.3%)	16 (94.1%)	28 (93.3%)
Thyroid diseases			
Present	3 (23.1%)	4 (23.5%)	7 (23.3%)
Absent	10 (76.9%)	13 (76.5%)	23 (76.7%)
Physically active			
Present	6 (46.2%)	9 (52.9%)	15 (50.0%)
Absent	6 (46.2%)	8 (47.1%)	14 (46.7%)
Missing	1 (7.7%)	0 (0%)	1 (3.3%)
Self-rated health status_preCOV			
Mean (SD)	74.7 (10.2)	84.2 (12.5)	80.1 (12.3)
Median [Min, Max]	80.0 [50.0, 86.0]	85.0 [68.0, 100]	80.0 [50.0, 100]
Home management			
Present	5 (38.5%)	9 (52.9%)	14 (46.7%)
Missing	0 (0%)	2 (11.8%)	2 (6.7%)
Hospital – O2 support			
Present	8 (61.5%)	5 (29.4%)	13 (43.3%)
Hospital - NIV, CPAP or IV			
Present	0 (0%)	1 (5.9%)	1 (3.3%)

SD: standard deviation; preCOV: before COVID-19; NIV: non-invasive ventilation. CPAP: continuous positive airway pressure; IV: invasive ventilation.

noninvasive ventilation (NIV) or invasive ventilation vs. 46.7% managed at home). The percentage of hospitalized patients reached 61.5% (8 of 13 participants) amongst patients aged more than 60 years old vs. 29.4% in the younger group. Of the eight patients affected by hypertension, six belonged to the subgroup of patients aged ≥ 60 years old and older (6 of 13 vs. 2 of 17, 27% of the whole sample). All the participants with heart diseases were older than 60 years (3 of 13 vs. 0 of 17, 3% of the whole sample). The rate of pulmonary diseases was higher in the older subgroup than in the younger one (4 of 13 vs. 2 of 17; 20% in the whole sample). Half of participants referred to have been physically active in the year prior to the admission to our service and similar mean BMI values were observed in both age subgroups. The level of self-reported health before COVID-19, evaluated with the visual analogue scale (VAS), was 80.1 and this score differed in the two subgroups (84.2 in the under 60 vs. 74.7 in the over 60).

Repeated Measure Paired T-Test Analysis were made to assess the differences means of collected measures (muscle strength and physical performance measures, body composition measures, bloods biochemistry measures and self-rated health measure) during t0 and after 28 days of daily consumption of a sachet of Apportal® (t1) (Table 2). Mean value of hand grip strength score in the whole sample increased significantly at 28.9 Kg at t1 (vs. 26.3 Kg at t0; $p < 0.05$) as did the mean time of strength exhaustion, which improved from 31.7 s (sec) at t0 to 47.5. When stratified by sex, differences in means of hand grip strength between t0 and t1 was still statistically significant amongst women.

Participants performed a significantly higher number of repetitions than at t1 at t0 (28.3 vs. 22.0; $p < 0.05$) during the one-minute chair stand test. None of the parameters of the body composition significantly improved, except for phase angle (t0, mean 5.50 ± 0.902 ; t1, mean 5.67 ± 0.807 ; $p = 0.01$). Among the blood biochemistry, we found a trend in reduction, although not statistically significant, in the ferritin levels before and after nutritional supplementation (94.4 vs. 84.3, respectively; $p = 0.08$). At t1, the self-rated health status increased by at least 13 points (t0, mean 57.6 ± 5.86 ; t1, mean 71.4 ± 6.73 ; $p < 0.05$).

4. Discussion

We conducted an exploratory evaluation to investigate the potential impact of a nutritional supplement on muscle strength and function in a small sample of COVID-19 survivors affected by fatigue. To the best of our knowledge, there are no previous studies that evaluate fatigue in terms of reduced tolerance on exercise among Covid-19 survivors with persistent symptoms in the post-acute phase. Our findings suggest an improvement of muscle strength and physical performance potentially related to the 28 days of supplementation with Apportal®.

Whilst limited by a small sample, we aimed to evaluate the impact of a nutritional supplement not only in hospitalized patients for COVID-19 but also in those home-managed. In fact, fatigue has been reported in more than 50% of not-hospitalized people affected by COVID-19 [11]. Nonetheless, the impact of COVID-19 on muscle function remains uncertain [43]. It is notable that prolonged hospitalization and the consequent immobilization can lead to muscle deterioration [44]. Tuzun et al. have demonstrated that women with severe acute illness showed worse grip strength values than non-severe COVID-19 cases [45]. At the same time, the loss of muscle function is estimated at approximately 0.8% per year starting from the fifth decade of life [46] and gradual decline in skeletal muscle mass and strength is around 2% per year starting from the sixth decade of life [47]. Some studies even reported a reduction in lean muscle mass by 3–8% per decade starting at age 30 [48]. The reduction in muscle strength, however, afflicts more

Table 2
Repeated Measure T-Test (Paired T-Test) Analysis on t0 datapoints and t1 datapoints (28 days after the daily assumption of the nutritional supplement Apportal®).

	t0 (N = 30)	t1 (N = 30)	p-values
Hand grip strength (Kg)			
Mean (SD)	26.3 (10.3)	28.9 (9.49)	<0.05
Median [Min, Max]	23.8 [13.3, 53.8]	24.7 [14.8, 49.9]	
Females			
Mean (SD)	21.9 (6.69)	24.7 (6.00)	<0.05
Median [Min, Max]	21.9 [13.3, 34.9]	24.7 (6.00)	
Males			
Mean (SD)	36.6 (10.4)	38.6 (9.24)	0.1501
Median [Min, Max]	37.2 [20.5, 53.8]	39.0 [21.8, 49.9]	
Hand grip exhaustion time (sec)			
Mean (SD)	31.7 (10.7)	47.5 (21.7)	<0.05
Median [Min, Max]	35.0 [10.0, 47.0]	45.0 [11.0, 102]	
One-min sit-to-stand test (nr. of repetitions)			
Mean (SD)	22.0 (5.86)	28.3 (6.73)	<0.05
Median [Min, Max]	22.5 [6.00, 35.0]	28.0 [17.0, 41.0]	
Self-rated health status			
Mean (SD)	57.6 (16.9)	71.4 (16.4)	<0.05
Median [Min, Max]	60.0 [30.0, 90.0]	75.0 [30.0, 98.0]	
SMM			
Mean (SD)	24.1 (4.86)	24.2 (4.55)	0.7612
Median [Min, Max]	23.0 [16.6, 36.4]	23.0 [16.1, 33.5]	
BFM			
Mean (SD)	20.4 (6.90)	20.0 (7.02)	0.2563
Median [Min, Max]	17.6 [10.9, 37.8]	18.0 [9.20, 36.6]	
BMR			
Mean (SD)	1330 (179)	1340 (173)	0.6343
Median [Min, Max]	1290 [1060, 1790]	1300 [1040, 1700]	
SMI			
Mean (SD)	7.07 (0.966)	7.11 (0.965)	0.5738
Median [Min, Max]	6.75 [5.60, 9.30]	7.00 [5.60, 8.80]	
Phase Angle			
Mean (SD)	5.50 (0.902)	5.67 (0.807)	0.01559
Median [Min, Max]	5.30 [3.50, 7.80]	5.50 [4.00, 7.80]	
Hemoglobin (g/dl)			
Mean (SD)	13.7 (1.56)	13.8 (1.72)	0.6403
Median [Min, Max]	13.7 [10.9, 17.5]	13.7 [10.5, 17.5]	
Ferritin (ng/ml)			
Mean (SD)	94.4 (99.8)	84.3 (83.7)	0.08022
Median [Min, Max]	56.0 [7.00, 464]	52.0 [5.00, 366]	
Iron (gamma/dl)			
Mean (SD)	79.9 (26.4)	80.4 (28.2)	0.9375
Median [Min, Max]	77.5 [36.0, 142]	80.0 [37.0, 165]	
Creatinine (mg/L)			
Mean (SD)	0.726 (0.163)	0.748 (0.188)	0.1011
Median [Min, Max]	0.680 [0.510, 1.27]	0.720 [0.520, 1.38]	
Albumin (g/L)			
Mean (SD)	41.4 (2.50)	41.6 (2.56)	0.704
Median [Min, Max]	41.0 [36.0, 46.0]	41.5 [37.0, 48.0]	
Liver enzymes ALT (GPT) (U/L)			
Mean (SD)	17.9 (7.60)	17.3 (7.22)	0.4545
Median [Min, Max]	16.0 [8.00, 40.0]	15.5 [8.00, 40.0]	
C Reactive Protein (mg/L)			
Mean (SD)	2.34 (4.48)	1.77 (2.16)	0.4774
Median [Min, Max]	0.650 [0.500, 23.0]	0.550 [0.500, 8.00]	

SD: standard deviation; SMM: skeletal muscle mass; BFM: body fat mass; BMR: basal metabolic rate; SMI: skeletal muscle index.

frequently older adults in terms of sub-standard grip strength score [49] and sarcopenia may be present in up to 5% aged 40–70 of individuals, according from UK Biobank data [50]. In this scenario, muscle loss and decrease of muscle strength could virtually affect people of all ages, especially within the context of COVID-19 pandemic. Furthermore, it is well known that consistent physical exercise and adequate dietary intake might prevent the loss of muscle function in vulnerable people [51,52]. Changes in diet and physical activity routines due to restrictions put in place to reduce the spread of the virus during the pandemic might have altered individuals' metabolism homeostasis, favoring the unbalance between anabolism and catabolism [53].

The probable effect of this nutritional supplement on muscle function derives from the combination of several nutrients, like magnesium, zinc, carnitine and arginine. The beneficial effect of magnesium on grip strength has been found in a small group of healthy middle-aged women after 8 weeks of co-supplementation with vitamin D [54]. A combination of physical exercise program and assumption of magnesium may also improve physical performance on Short Physical Performance Battery (SPPB) [29]. Unfortunately, no significant results on body composition emerged from our analysis. Probably, magnesium may improve skeletal mass [55] but the short time interval between the start of nutritional supplementation and the control visit (t1) does not allow us to assess any increase in lean mass or SMI. Furthermore, another clinical trial has analyzed the role of carnitine in the improvement of frail status among older people and has shown its potential effect on muscle mass of vulnerable patients [56]. Also, the role of arginine is particularly evident on young ages, in which its daily assumption may maintain or ameliorate functional parameters of physical performance [57,58].

Finally, we reported a significant increase in mean value of self-rated health at the control visit compared to t0. A Korean study revealed that low grip strength is associated with low quality of life in many items [59]. The importance of improving muscle strength to maintain adequate levels of quality of life is particularly evident among older adults [60]. Indeed, our study revealed that at the first evaluation the older subgroup reported a lower score of self-rated health in the VAS. Beyond the quarantine for the Sars-CoV-2 seropositivity, the government restrictions have exposed vulnerable people to social isolation or loneliness [61]. The improvement of muscle function seen in our participants after assuming the nutritional supplement may explain the consequent increase in self-rated health status.

This work has several limitations. The major limitation is represented by the absence of a control group and the limited study sample, especially males. For these reasons, a more in-depth analysis was not possible. Moreover, because of the intrinsic nature of the study, we cannot undermine the role of confounding factors, such as compliance to the supplementation. Low-intensity aerobic training exercises might have improved the hand grip strength score after COVID-19 [62]. In fact, more than 50% of our sample was physically active at the time of the evaluation and we cannot rule out the possibility that participants might have changed lifestyle habits, including diet and outdoor activities, after being motivated by taking the nutritional supplement at the first visit. Finally, a longer period since the first COVID-19 diagnosis might have independently helped to ameliorate the physical wellbeing of the patients. Despite these limitations, our data reveal interesting results and provide a basis for future and wider studies that could identify the best therapeutic options for the treatment of fatigue and its physical implications in the post-acute COVID-19. Considering that it was a single-center study, designed on a small group of COVID-19 survivors from the same geographic area, our results need to be reproduced on large scale to confirm the effectiveness of this nutraceutical on physical implication of COVID-19 fatigue. A continuation of treatment with nutritional supplements based on magnesium, zinc, carnitine and arginine beyond the suggested 28 days could lead to further improvement in muscle function.

In conclusion, we evaluated the potential effect of Apportal® in a small group of COVID-19 survivors affected by fatigue with reduced physical tolerance to exercise. After 28 days of daily assumption of this nutritional supplement, we found a significant difference in means between the control visit and the first visit of muscle strength and physical performance, in term of higher values on grip strength, major numbers of repetitions on the one-min sit-to-stand test, and longer handgrip exhaustion time. Moreover, all

sample reported enhancement of self-rated health status over the study period and this may be associated to the nutritional supplementation. Future interventional studies are warranted to confirm whether the combination of these nutrients might improve parameters of muscle function and quality of life in COVID-19 survivors.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore of Rome, Italy (IRB number: 32/20).

Consent for publication

The author gives consent for publication of this paper.

Availability of data and material

All the data and material are available.

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CRedit author statement

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Declaration of competing interest

None of the participants in the Gemelli Against COVID-19 Post-Acute Care Study Group has any conflict of interest. Pharmanutra is the pharmaceutical company that has the rights of the nutritional supplement Apportal®. Authors declare that Pharmanutra had not influenced participants' choices and had no role in the study design and data interpretation.

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Appendix. The Gemelli Against COVID-19 Post-Acute Care Study Group is composed as follows:

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- Internal Medicine team: Stella Leonardo, Addolorato Giovanni, Franceschi Francesco, Mingrone Gertrude, Zocco MA.

- Microbiology team: Sanguinetti Maurizio, Cattani Paola, Marchetti Simona, Posteraro Brunella, Sali M.

- Neurology team: Bizzarro Alessandra, Lauria Alessandra.

- Ophthalmology team: Rizzo Stanislao, Savastano Maria Cristina, Gambini G, Cozzupoli GM, Culiarsi C.

- Otolaryngology team: Passali Giulio Cesare, Paludetti Gaetano, Galli Jacopo, Crudo F, Di Cintio G, Longobardi Y, Tricarico L, Santantonio M.

- Pediatric team: Buonsenso Danilo, Valentini P, Pata D, Sinatti D, De Rose C.

- Pneumology team: Richeldi Luca, Lombardi Francesco, Calabrese A, Leone Paolo Maria, Calvello Maria Rosaria, Intini Enrica, Montemurro Giuliano.

- Psychiatric team: Sani Gabriele, Janiri Delfina, Simonetti Alessio, Giuseppin G, Molinaro M, Modica M.

- Radiology team: Natale Luigi, Larici Anna Rita, Marano Riccardo.

- Rheumatology team: Paglionico Annamaria, Petricca Luca, Gigante Luca, Natalello G, Fedele AL, Lizzio MM, Tolusso B, Di Mario Clara, Alivernini S.

- Vascular team: Santoliquido Angelo, Santoro Luca, Di Giorgio Angela, Nesci Antonio, Popolla V.

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