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Covid-19

Nutritional status in post SARS-Cov2 rehabilitation patients

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SUMMARY

Background & aims: After prolonged hospitalization, the assessment of nutritional status and the identification of adequate nutritional support is of paramount importance. In this observational study, we aimed at assessing the presence of a malnutrition condition in SARS-Cov2 patients after the acute phase and the effects of a multidisciplinary rehabilitation program on nutritional and functional status.

Methods: We recruited 48 patients (26 males/22 females) admitted to our Rehabilitation Unit after discharge from acute Covid Hospitals in northern Italy with negative swab for SARS-Cov2. We used the Global Leadership Initiative on Malnutrition (GLIM) criteria to identify patients with different degrees of malnutrition. Patients underwent a 3 to 4-week individual multidisciplinary rehabilitation program consisting of nutritional intervention (energy intake 27to30 kcal/die/kg and protein intake 1−1.3 g/die/kg), exercise for total body conditioning and progressive aerobic exercise with cycle- and arm-ergometer (45 min, 5 days/week). At admission and discharge from our Rehabilitation Unit, body composition and phase angle (PhA) (BIA101 Akern), muscle strength (handgrip, HG) and physical performance (Timed-Up-and-Go, TUG) were assessed.

Results: At admission in all patients the mean weight loss, as compared to the habitual weight, was −12.1 (7.6)%, mean BMI was 25.9 (7.9) kg/m^2, mean Appendicular Skeletal Muscle Index (ASMI) was 6.6 (1.7) kg/m^2 for males and 5.4 (1.4) kg/m^2 for females, mean phase angle was 2.9 (0.9)°, mean muscle strength (HG) was 21.1 (7.8) kg for males and 16.4 (5.9) kg for females, mean TUG value was 23.7 (19.2) s. Based on GLIM criteria 29 patients (60% of the total) showed a malnutrition condition. 7 out of those 29 patients (24%) presented a mild/moderate grade and 22 patients (76%) a severe grade. After a rehabilitation program of an average duration of 25 days (range 13−46) ASMI increased, with statistically significant differences only in females ($p = 0.001$) and HG improved only in males ($p = 0.0014$). In all of the patients, body weight did not change, CRP/albumin ($p < 0.05$) and TUG ($p < 0.001$) were reduced and PhA increased ($p < 0.01$).

Conclusions: We diagnosed a malnutrition condition in 60% of our post SARS-Cov2 patients. An individualized nutritional intervention with adequate energy and protein intake combined with tailored aerobic and strengthening exercise improved nutritional and functional status.

1. Introduction

Covid-19 is a systemic disease due to a coronavirus called SARS-CoV-2 that cause severe acute respiratory syndrome and multi-organ failure [1]. In Italy, during the pandemic peak in March 2020, 12% of all infected patients was admitted to Intensive Care Units (ICU) [2]. The presence of different chronic diseases, including

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hypertension, diabetes, obesity, cancer, cardiovascular and chronic lung diseases were demonstrated as independent risk factor for SARS-CoV-2 infection considering the severity of the manifestations and negative outcome [3]. The nature of this association might be due to different mechanisms: immunologic response, metabolic disorders and endothelial dysfunction.

Acute or chronic inflammation might induce malnutrition [4]. In SARS-Cov2 patients, the development of poor nutritional status is probably due to a direct effect of the virus and the fragility of these patients for the presence of other infections or systemic organ failure [5]. The risk of nutritional deficiency depends on the presence of gastro-enteric symptoms, such as nausea, vomiting and persisting dysphagia and is related to lengthy hospital stay, first in ICU with prolonged immobilization and then in post-acute hospitals [6]. Post SARS-Cov2 patients experience an increased disability for the negative metabolic and neurologic consequences of malnutrition, e.g. a reduction in skeletal mass and function [6,7].

Therefore, diagnosis and treatment of malnutrition appear of paramount importance in the management of post SARS-Cov2 patients to improve their rehabilitation outcomes and long term prognosis [1]. In this observational study, we aimed at: 1) diagnosing a possible malnutrition condition according to the most recent criteria in patients admitted for a post-Covid multidisciplinary rehabilitation program; 2) assessing the effectiveness of an individualized multidisciplinary rehabilitation program, including adequate nutritional and physical exercise interventions, on nutritional and functional status in post SARS-Cov2 patients.

2. Materials and methods

2.1. Subjects

We consecutively recruited patients admitted to our Rehabilitation Unit from April to June 2020 after they had been discharged from different Covid Hospitals in northern Italy. All of the patients presented a history of SARS-Cov2 infection documented by positive swabs at the real-time PCR and next-generation sequencing and with different clinical manifestations. All presented two consecutive negative swabs for SARS-Cov2 before being admitted to our Rehabilitation Unit. This study was conducted according to the World Medical Association Declaration of Helsinki and was approved by Ethics Committee of Istituto Auxologico Italiano (#2020_05_19_04). Written informed consent was obtained from all experimental patients.

2.2. Clinical data

Patients' demographic characteristics, presence of comorbidities and clinical course of the SARS-Cov2 infection, with particular reference to intubation, non-invasive ventilation and pharmacological treatment, were extracted from the medical record.

2.3. Anthropometric parameters

Body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) were measured in light indoor clothing. Body mass index (kg/m^2) was calculated. At admission, individual weight loss was calculated from the body weight value prior to the SARS-Cov2 infection, held as “habitual body weight”. Body composition was assessed in the morning in a quiet room at a temperature of 22–25 °C with bioimpedentiometry (BIA 101/s, Akern® – Firenze, Italy) with the patient in a supine position with lower limbs slightly apart and empty bladder. Whole-body resistance (*Rz*) and reactance (*Xc*) were measured by skilled operators with impedance analyser which emitted 50 kHz alternating sinusoidal current connected to four surface electrodes placed on the right hand and foot [8]. To assess the Appendicular Skeletal Muscle Mass (ASM) we used the two following formulas:

- ASM beyond 65 years = −4.211 + (0.267*height^2/Rz) + (0.095*weight) + (1.909*gender (male = 1, female = 0)) + (0.012*age) + (0.058*Xc) [9];
- ASM over 65 years = 3.964 + (0.227*RI) + (0.095*weight) + (1.384*gender) + (0.064*Xc),

where *RI* indicate *Rz* normalized for height [10]. We adjusted ASM by body height (ASM/height^2), in accordance to Cruz-Jentoft et al. [11], to define the appendicular skeletal muscle mass index (ASMI). The cut-off values from the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) were used to diagnose sarcopenia: ASMI <7 (kg/m^2) for males and ASMI <5.5 (kg/m^2) for females. We also assessed the Phase Angle (PhA), a derived measure obtained from the equation: Phase angle (degrees) = arctan(Xc/R) × (180/π) [12]. Despite variability in PhA due to gender (higher values in males than females), aging and BMI >40 kg/m^2 [13], it is acknowledged that low PhA values (<5°) are associated with poor nutritional status and outcome [12].

We measured muscle strength and performance values with the handgrip (HG) and Timed-up-and-go (TUG) tests, respectively. We used a Jamar Analogue Hand Dynamometer (Asimow Engineering Co., Los Angeles, CA, USA) to measure strength. The mean value of three grip strength repetitions for each hand was used [14] and compared to the existing normative values for males (>27 kg) and females (>16 kg) [11]. Physical performance was evaluated with the TUG test [15]: a TUG value over 12 s is considered as a practical cut-off for a low performance [16], values ≥20 s indicate severe sarcopenia [11].

2.4. Laboratory findings

Hematic/chemical parameters were detected with DXH600 (Bachman Coulter, Germany) and COBAS 6000 (Hoffmann-La Roche, CH). We analyzed blood count (HB, GB and L), ferritin, C-reactive protein (CRP), aPTT, D-dimer, total cholesterol (TC), LDH, total proteins, albumin, glycemia, B12 and D_3(25OH) vitamin, calcemia and creatinine. We calculated the levels of albumin adjusted for inflammation markers (CPR/albumin ratio) that we used as etiological criteria in the evaluation of malnutrition [17]. Previous studies considered CPR/albumin ratio an index that correlated positively with infection, i.e., a higher ratio indicates inflammatory status [20]. Two recent studies defined a cut-off value for CRP/albumin ratio at 0.07 [18] and 0.08 [19]. For the present investigation we decided to adopt the lower value (0.07).

2.5. Assessment of nutritional risk and diagnosis of malnutrition

Recently, the clinical nutrition Societies worldwide introduced the GLIM (Global Leadership Initiative on Malnutrition) criteria for the diagnosis of malnutrition [20]. GLIM is a two-step approach: firstly, it evaluates the risk of malnutrition utilizing a validate screening tool, and, secondly, if a nutritional risk is present, it formulates the diagnosis and grades the severity of malnutrition.

2.5.1. First step

The nutritional risk was assessed within 24 h from admission using the NRS-2002, as recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) [1]. The score (range 0–6) is divided into two sub-scores (nutritional status with range 0–3 and comorbidities with range 0–3). We assigned a score of 2 in the comorbidities sub-score when severe consequences of SARS-

Cov2 infection were present. An extra 1 point was then added to the total score if the patient was ≥70 years of age. Total scores ≥3 defined patients with nutritional risk requiring a nutritional care plan.

2.5.2. Second step

As for the GLIM criteria, a combination of at least one phenotypic criterion and one etiologic criterion is required for malnutrition diagnosis according to the GLIM criteria. Weight loss, low BMI, and reduced muscle mass were classified into phenotypic criteria. Weight loss was calculated respect the habitual body weight, we considered a weight loss >5% of the habitual body weight in the past 6 months as phenotypic criteria. The reference (<20 if <70 year, or <22 if >70 year) was used to define low BMI. The definition of reduced muscle mass was based on a low ASMI (ASMI < 7 (kg/m^2)) for males and (ASMI < 5.5 (kg/m^2)) for females. Normally GLIM etiologic criterion consisted of reduced food intake/assimilation and disease burden/inflammation [20]. Since most patients presented with various symptoms (e.g. dysphagia, gastrointestinal etc), the definition of an etiologic criteria was difficult. For such reason, we opted for using a laboratory inflammation marker, the CPR/albumin ratio [20] and we considered a cut off of 0.07 as a presence of inflammation [18]. To define the degree of severity of malnutrition in 2 stages according to GLIM, we considered the extent of phenotypic criteria reported by GLIM.

2.6. Rehabilitation program

In line with the Stanford Hall consensus statement for post-COVID-19 rehabilitation [21], our multidisciplinary program aimed at recovering the impairment and functional limitation of the respiratory, cardiac, musculoskeletal and neurological systems. It included psychiatric support, cognitive behavioral therapy to reduce post-traumatic stress symptoms, and nutritional therapy to enhance malnutrition either as a direct consequence of the infection or as indirect result of treatments. Duration of the program was on average 25 days.

2.6.1. Nutritional therapy

Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) developed a practical guide for the nutritional management of patients with SARS-CoV2 infection [1]. The expert panel suggested a nutritional program containing specific quantities of macronutrients (protein, fat and carbohydrate) and micronutrients (vitamins or minerals) based on the nutritional needs of each patient. Total energy intake was calculated in the range between 27 and 30 kcal/die/kg considering the adjusted body weight (AjBW = ideal body weight + ((actual body weight − ideal body weight)*0.33)) [22] for BMI >28 kg/m^2 or the habitual body weight for BMI <28 kg/m^2 before SARS-Cov2 infection. Similarly, we calculated protein intake in the range between 1 and 1.3 g/die/kg of body weight. An optimal fat/carbohydrate energy ratio was 30:70, or 50:50 in O_2 supplemented patients. Furthermore, as recommended by ESPEN Guidelines, patients received oral multivitamin supplementation (vitamin A, D, E K, C and B vitamins), essential amino acids, minerals (NA^+, K^+, Ca^+, P, Mg, Mn, MO, Se, Cr, I, Fe, Zn, Cu), carnitine and probiotics (*Streptococcus thermophilus*; *Bifidobacterium breve*; *Bifidobacterium longum*; *Bifidobacterium infantis*; *Lactobacillus acidophilus*; *Lactobacillus plantarum*; *Lactobacillus paracasei*; *Lactobacillus delbrueckii* subsp. *bulgaricus*). In patients with reduced oral diet intake of proteins, supplementation with different components of whey or vegetable proteins were used to cover the daily need amount. Two patients were treated with complete enteral nutrition: one of them presented tracheostomy and the other swallowing neurological disorder.

2.6.2. Physical exercise

Each patient was individually guided to perform sit-to-stand, simple bed exercises for upper body conditioning [7,23] and progressive limb muscle strengthening (8–12 repetitions, 1–3 sets with 2 min rest between sets). After few days, progressive aerobic exercise with cycle- and arm-ergometer was introduced. The latter was performed at moderate intensity, namely, 65% of maximal heart rate based on the equation [(220-age) × 0.65]. Such approach was individualized based on the patient's conditioning status and perception of effort. The target total training volume was 45 min/session, 5 sessions/week.

2.6.3. Outcomes

To evaluate the effectiveness of the rehabilitation program, clinical evaluation, anthropometrics, laboratory data, body composition (ASMI and PhA), muscle strength (HG) and performance tests (TUG) were assessed at admission and before discharge.

2.7. Statistical analysis

Continuous variables were expressed as mean ± SD values. Differences between groups were assessed using a Mann–Whitney U test for continuous variables, or $\chi 2$ test for categorical data as appropriate. A P value < 0.05 was considered to be statistically significant. Statistical analyses were performed with SPSS 25.0 (IBM, USA).

3. Results

At the baseline we assessed 48 post SARS-Cov2 patients (M/F 26/22), mean age was 68.7 (11.8) years, mean BMI was 25.9 (7.9) kg/m^2. The 27.1% of them were overweight (25 < BMI <29.9 kg/m^2) and 18.8% obese (BMI ≥30.0 kg/m^2). In the 3 months before the SARS-Cov2 infection, the mean habitual body weight was 81.90 (25.1) kg. Fourteen of them (28.6%) had been discharged from ICU. At admission in our Rehabilitation Unit, mean body weight was 71.8 (22.6) kg, with a mean weight loss of −12.1 (7.6)% (Table 1). The most common comorbidities were hypertension (12.2%), diabetes (26.5%), cardiovascular (38.8%), cerebrovascular (26.5%) and lung chronic diseases (10.2%).

Muscle strength (HG test) showed low levels both in men and women, mean values 21.1 (7.8) kg and 16.4 (5.9) kg, respectively. HG met the criteria for probable sarcopenia in 14 male and 9 female patients. The BIA analysis measured low ASMI values of 6.6 (1.7) kg/m^2 for males and 5.4 (1.4) kg/m^2 for females, as compared to the normative values. TUG showed a mean time of 23.7 (19.2) s that met the criteria for severe sarcopenia diagnosis. Based on the results of BIA analysis and TUG test, 14 patients (8 male and 6 female) met the criteria for the diagnosis of sarcopenia, and 8 of them (4 male and 4 female) presented with severe sarcopenia, in accordance with Cruz-Jentoft et al. [24]. All patients also showed a mean PhA of 2.9 (0.9)°. PhA values <5° have been shown to correlate with a condition of malnutrition [12]. As for laboratory findings: red, white blood cell and lymphocyte count were within the normal range [4.2 (0.6) × 10^{12}/l, 6.7 (2.1) × 10^9/l and 2.2 (1.1) × 10^9/l, respectively]; coagulation indexes, such as D-dimer [1102.5 (1212.1) ng/ml] and aPTT [1.189 (0.283) s] were increased; the inflammatory marker ferritin was in the upper range [423.7 (390.8) ng/ml]. Nutritional markers as hemoglobin [12.3 (1.6) g/dl], glycemia [96.7 (16.0) mg/dl], iron [67.4 (25.6) mg/dl], HDL [42.3 (12.9) mg/dl], calcium [12.4 (19.1) mg/dl], vitamin B12 [461.6 (239.3) pg/l] showed normal values and vitamin D_3(25OH) was reduced [19.4 (14.4) ng/ml]. Albumin levels were low [mean 3.8 (0.5) mg/dl, range 3.3–5 mg/dl] with increased levels of CRP [mean

Table 1
Main clinical variables collected in all patients at baseline.

	Mean (sd)	Range
Sex n° (M/F)	26/22	
Age (yrs)	68.7 (11.8)	43–93
Weight (kg)	71.8 (22.6)	41.5–161.3
BMI (kg/m^2)	25.9 (7.9)	16.6–56.1
Weight loss (% of initial weight)	−12.1 (7.6)	0.5–27.9%
ASMI (kg/m^2)		
M	6.6 (1.7)	4.5–12.1
F	5.4 (1.4)	3.9–9
PhA (°)	2.9 (0.9)	1.5–4.7°
White blood cell (10^9/l)	6.7 (2.1)	
Red blood cell (10^{12}/l)	4.2 (0.6)	
Hb g/dl	12.3 (1.4)	
Lymphocyte (10^9/l)	2.2 (1.1)	
CRP (mg/dl)	1.0 (1.3)	
Albumin g/dl	3.8 (0.5)	
CRP/albumin (mg/dl)	0.3 (0.4)	
Iron (mg/dl)	67.4 (25.6)	
Ferritin (ng/ml)	423.7 (390.8)	
B12 (pg/l)	461.6 (239.3)	
P-aPTT (s)	1.189 (0.283)	
D-dimer (ng/ml)	1102.5 (1212.1)	
HDL (mg/dl)	42.3 (12.4)	
Calcium (mg/dl)	12.4 (19.1)	
Glycemia (mg/dl)	67.4 (25.6)	
D_3(25OH) (ng/ml)	19.4 (14.4)	
HG (kg)		
M	21.1 (7.8)	6.0–36.9
F	16.4 (5.9)	9.7–30.8
TUG (s)	23.7 (19.2)	8.3–83.3

Mean values + (SD) of all 48 patients at hospital admission. BMI (Body Mass Index); ASMI (Appendicular Skeletal Muscle Index); PhA° (Phase Angle); HG: Handgrip; TUG (Timed-up-and-go tests).

Table 3
Main clinical variables collected in malnourished patients at baseline and discharge.

	T0 (SD)	T1 (SD)	*p*-value
Sex n° (M/F)	18/11		
Age (yrs)	70.1 (10.1)		
Weight (kg)	72.3 (25.9)	72.8 (25.3)	0.225
BMI (kg/m^2)	25.8 (9.5)	25.9 (9.2)	0.293
Weight loss (%)	13.7 (6.8)		
ASMI (ASM/height^2) (kg/m^2)			
M	6.7 (1.9)	7.1 (2.5)	0.342
F	5.2 (2.0)	5.8 (2.0)	0.001
PhA (°)	2.5 (0.8)	3.5 (0.9)	0.008
White blood cell (10^9/l)	7.2 (1.7)	6.8 (2.5)	0.354
Red blood cell (10^{12}/l)	4.1 (0.6)	4.2 (1.1)	0.240
Hb g/dl	12.0 (1.4)	12.5 (2.9)	0.025
Lymphocyte (10^9/l)	2.2 (0.9)	2.3 (0.9)	0.257
CRP (mg/dl)	1.6 (1.5)	0.9 (1.1)	0.015
Albumin g/dl	3.6 (0.4)	3.8 (0.3)	0.003
CRP/albumin (mg/dl)	0.5 (0.5)	0.3 (0.3)	0.011
Iron (mg/dl)	62.2 (24.0)	79.3 (42.51)	0.316
Ferritin (ng/ml)	552.3 (417.7)	361.2 (329.1)	<0.001
B12 (pg/l)	473.9 (308.3)	477.1 (285.1)	0.996
P-Apptt (s)	1.2 (0.3)	1.7 (2.1)	0.283
D-dimer (ng/ml)	1435.8 (1441.9)	776.6 (778.0)	0.017
HDL (mg/dl)	40.6 (12.6)	40.5 (13.7)	0.388
Calcium mg/dl	14.3 (24.9)	14.9 (27.1)	0.315
Glycemia (mg/dl)	98.7 (16.2)	92.9 (23.7)	0.107
D_3(25OH) (ng/ml)	16.4 (10.9)		
Handgrip (kg)			
M	23.3 (7.5)	26.7 (7.8)	0.014
F	16.6 (7.3)	17.8 (6.4)	0.223
TUG (s)	25.4 (19.5)	16.3 (15.9)	<0.001

Mean values + (SD) of the 29 malnourished patients at T0 (admission time) and after intervention T1 (discharge time). BMI (Body Mass Index); ASMI (Appendicular Skeletal Muscle Index); PhA° (Phase Angle); HG: Handgrip; TUG (Timed-up-and-go tests).

1.0 (1.3) mg/dl, range 0.1–4.3 mg/dl]; the albumin levels adjusted for inflammation markers resulted only mildly increased [CRP/albumin mean 0.299 (0.408) mg/dl] (Table 1). The assessment of nutritional risk according to NRS-2002 identified 10 patients with mild or moderate risk (score 1 or 2) and 38 patients with severe nutritional risk (score $\geq$ 3).

Considering the GLIM criteria, a diagnosis of malnutrition was present in 29/48 (60.41%) patients, as reported in Table 2. Seven out of those 29 patients (24%) presented a mild/moderate grade and 22 patients (76%) a severe grade (Table 2).

3.1. Rehabilitation

During the rehabilitation program, 29 patients with malnutrition (Table 3) underwent a nutritional program with a mean energy intake of 1770.69 (341.61) kcal/die (range 1300–2600) or 27.5 (3.7) kg/die and a mean protein intake of 79.5 (14.9) g/die (range 55–120) or 1.25 (0.2) g/die/kg (range 0.9–1.5). At baseline, the 29 malnourished patient reported a lower level of D_3(25OH) vitamin (ng/ml) 16.4 (10.9), HDL (mg/dl) 40.6 (12.6), Iron (mg/dl) 62.2 (24.0) and a higher level of glycemia (mg/dl) 98.7 (16.2), Ferritin (ng/ml) 552.3 (417.7), CRP/albumin (mg/dl) 0.5 (0.5) (Table 3).

Table 2
Malnourished patients according to GLIM.

Severity grading of malnutrition into stage 1 (moderate) and stage 2 (severe) malnutrition	
Stage 1/Moderate Malnutrition	7 patients
Stage 2/Severe Malnutrition	22 patients

Patients diagnosed as malnourished and divided in stage 1 or stage 2 based on the severity of malnutrition according to the GLIM score.

At discharge, body weight did not change significantly [72.3 (25.9) VS 72.8 (25.3) kg BMI 25.8 (9.5) vs 25.9 (9.2) kg/m^2], while body composition registered a significant increase in ASMI only in females [M 6.7 (1.9) vs 7.1 (2.5) kg/m^2, $P = 0.342$; F 5.2 (1.99) vs 5.8 (2.0) kg/m^2, $p = 0.001$] and a significant increase in PhA values [mean 2.5 (0.8) vs 3.5 (0.9)°, $p < 0.01$]. We also registered increases in muscle strength (HG) that reached statistical significance only in males [23.3 (7.5) vs 26.7 (7.8) kg, $p = 0.014$] and not in females [16.6 (7.3) vs 17.8 (6.4) kg, $p = 0.223$]. Physical performance capacity increased significantly as shown by a reduction in TUG test values [25.4 (19.5) vs 16.3 (15.9) s, $p < 0.001$]. A significant reduction in ferritin levels [552.3 (417.7) vs 361.2 (329.1) ng/ml, $p < 0.001$], D-dimer [1435.8 (1441.9) vs 776.6 (778.0) ng/ml, $p < 0.05$], CRP/albumin ratio [mean 0.5 (0.5) vs 0.3 (0.3) mg/dl, $p < 0.05$] due to a reduction in CRP [mean 1.6 (1.5) vs 0.9 (1.1) mg/dl, $p < 0.05$] and an increase of albumin levels [mean 3.6 (0.4) vs 3.8 (0.3) mg/dl, $p < 0.05$] and an increase in Hb [12.0 (1.4) 12.5 (2.9) g/dl, p < 0.05] were also observed.

4. Discussion

In this study, we documented a risk of malnutrition in post-acute SARS-Cov2 patients with low BMI and significant weight loss in the last months. According to the ESPEN criteria for the risk of malnutrition, based on NRS-2002, 38 of our post SARS-Cov2 patients presented a risk of malnutrition and need of nutritional care plan (NRS score $\geq$ 3) at admission in our Rehabilitation Unit, while the other patients 10 required only a weekly rescreening.

The clinical evaluation according to the GLIM criteria defined the diagnosis of malnutrition in 60.41% (29/48) of our post-acute SARS-Cov2 patients, whose severe in 22/29 (76%) presented with severe malnutrition. Factors known to contribute to malnutrition are: a decreased nutritional intake, an increased energy and protein

requirement, body weight loss, immobilization due to prolonged hospitalization in acute care, an inflammatory status.

Based on ASMI and PhA data and in accordance with the GLIM criteria, we could speculate that among the factors that cause malnutrition loss in metabolic cellular mass may play a role. In our study, cellular health, cell integrity and cell function were evaluated with PhA [25] and values below the 5th PhA percentile indicate a higher risk for malnutrition and mortality, as recently reported [26].

In SARS-Cov2 patients, the higher rates of pre-existing comorbidities, may also account for the development of malnutrition. In our sample, prevalence was 17.1% for hypertension, 16.4% for cardiac-cerebrovascular disease and 9.7% for diabetes [22]. Pre-existing chronic inflammation and activated immunological cell response with elevated levels of cytokines, multiorgan damage with possible tissue hypoxemia due to a reduced oxygen uptake and endothelial damage may all play a role in metabolic/nutritional dysfunctions in different pathways.

Based on our findings, possible determinants of malnutrition in SARS-Cov2 patients include: 1) severe body weight loss and low ASMI 2) persistent inflammatory condition, as documented by CRP, increased CRP/albumin ratio and ferritin levels; 3) pre-existing comorbidities, 4) pro-coagulation condition, sustained by high D-dimer plasma levels.

This condition appears to be related to persisting inflammation and altered nutrition indexes in the post-acute phase. In our study, the incidence of malnutrition in elderly patients with SARS-Cov2 was higher as previously reported [27]. Similar data had been reported [28] in severe and critically-ill SARS-Cov2 patients.

Age might be an important risk factor because it is demonstrated that the “inflamm-aging” condition with elevated levels of local and systemic pro-inflammatory cytokines, amplifies the “cytokine storm” with multiple organ failure [29]. A loss in lean mass was documented with CT scans in post- SARS-Cov2 obese and non-obese patients after lengthy hospitalization or ICU [30]. Some authors [27] tried to explain such effects with albumin and muscle protein consumption from acute inflammatory response to the infection and the production of cytokines. In fact, infecting viral pathogens modify the metabolic activity of host cells to favor viral replication, thereby disturbing the “normal” homeostasis of cellular metabolism [31]. The “cytokine storm”, liberating pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, and TGFβ) or chemokines (CCL2, CXCL10, CXCL9, and IL-8), is the acute response after the infection from different type of immunological cells (monocyte-macrophages, T or B cells [32]) which have a modulating-metabolic activity [33]. The catabolic effect of cytokines alter the metabolic pathways in the muscle, liver and adipose tissue, and contribute to protein caloric malnutrition [30]. The glycolysis pathway, tricarboxylic acid (TCA) cycle and lipid metabolism, are crucial for cell proliferation and viral replication and are modulate by virus reprogramming of host cells [34] or “cytokine storm”.

As previously demonstrated, elevated parameters of inflammation and high nutritional risk were independently associated with hypo-albuminemia [35]. Involuntary weight loss in this kind of patients is a strong predictor of negative outcomes. The individual multidisciplinary Rehabilitation program with tailored nutritional and physical exercise interventions, partially restored the condition of malnutrition and improved the impaired physical capacity. After 3–4 weeks of rehabilitation, reduction of the “cytokine storm” and protein supplementation to restore energy needs have shown to improve nutritional status. In fact, we registered a significant decrease in CRP and a slight increase in albumin levels, probably as the result of protein and caloric nutritional intervention. As for micronutrients supplementation, correction of vitamin D3 deficiency has been held as a preventive measure for SARS-CoV-2 infection [22].

Adequate energy and protein intakes used during rehabilitation induced no significant changes in body weight but an improvement of the condition of malnutrition was evident. As previously reported in other post-acute events such as ischemic stroke and hip fracture or in chronic inflammatory diseases such as chronic obstructive pulmonary disease, a high malnutrition risk was associated to increased clinical complications and mortality. The protein-caloric nutrition with or without supplementation leads to improvements in patients' strength and physical performance capacity [36]. In fact, as for body composition, we observed an increase in ASMI in females and an increase in PhA, particularly in severely malnourished patients. PhA is considered a feasible screening tool for the identification of patients with impaired nutritional and functional status [25].

A consequence of malnutrition is muscle dysfunction, as reflected by a decreased muscle strength [37] and increase in TUG time [38]. In post SARS-CoV-2 patients, a significant reduction in physical performance such as 6-min walking test and handgrip strength has already been documented [39]. This deconditioning may not only be due to muscle disuse atrophy. We know that “systemic inflammatory response syndrome” produces a severe oxygen debt at parenchymal level contributing to multiple organ dysfunction with the development of a possible critical polyneuropathy and myopathy [40]. In this contest, a cachectic myopathy due to malnutrition reduces functional performance. As previously described in anorexia nervosa, severe weight induces loss protein-energy malnutrition and muscle dysfunction. In muscle biopsies of anorexic patients, an increase in glycogen content was found, due to a defect in anaerobic glycolysis rather than a consequence of the loss of contractile proteins [41]. Our 3–4 week rehabilitation program significantly improved muscle strength (HG), physical performance (TUG), and body composition (ASMI), as assessed by BIA.

4.1. Limits of the study

Our study present some limits. Study sample size was low. We did not calculate it *a priori* because we enrolled patients admitted to the hospital during a limited period of the pandemia. Therefore, our data need to be confirmed by larger epidemiological studies and follow up studies. Lacking other measure of inflammatory markers, such as IL-1 or 6, describing possible correlations between the various malnutrition indexes was not possible. Furthermore, we did not take into consideration other risk factors pre-existing to the SARS-Cov2 infection, such as lifestyle, nutritional habits and physical activity levels may have also affected the nutritional conditions of our patients.

Nutritional status may play a role as prognostic factor for functional recovery. For this reason, the assessment of nutritional status and the identification of an adequate nutritional support is of paramount importance to optimize rehabilitation programs. Given the consequences of SARS-CoV-2 infection, we suggest to consider all patients in the post-acute phase as patients at risk of malnutrition, independently from body weight, BMI and age. Nutritional surveillance using specific screening, especially in patients with comorbid conditions, is necessary for an early diagnosis of malnutrition and timely nutritional therapy in order to improve functional recovery and long-term prognosis.

Authorship

Gobbi M participated in conceptualization, data collection and writing of the original draft. Brunani A participated in conceptualization, methodology, supervision, review and editing. Arreghini M, Baccalaro G and Brugliera L participated in clinical care of the patients, data collection and editing of the manuscript. Lucchetti E, Barbaglia M, Cova A, Fornara E, Galli S, participated in clinical care of the patients and data collection. Cimolin V participated in data

analysis. Dellepiane D participated in clinical care of the patients, review and editing. La Vela V participated in clinical care of the patients, conceptualization and writing of the original draft. Capodaglio P participated in project administration, clinical care of the patients, supervision, review and editing of the manuscript.

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Conflict of interest

All the authors declare no conflicts of interests.

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