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## Original article

# COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: A *post-hoc* analysis of a prospective cohort study



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## SUMMARY

**Background & aims:** Coronavirus disease 2019 (COVID-19) may associate with clinical manifestations, ranging from alterations in smell and taste to severe respiratory distress requiring intensive care, that might associate with weight loss and malnutrition. We aimed to assess the incidence of unintentional weight loss and malnutrition in COVID-19 survivors.

**Methods:** In this *post-hoc* analysis of a prospective observational cohort study, we enrolled all adult (age  $\geq 18$  years) patients with a confirmed diagnosis of COVID-19 who had been discharged home from either a medical ward or the Emergency Department of San Raffaele University Hospital, and were re-evaluated after remission at the Outpatient COVID-19 Follow-Up Clinic of the same Institution from April 7, 2020, to May 11, 2020. Demographic, anthropometric, clinical and biochemical parameters upon admission were prospectively collected. At follow-up, anthropometrics, the mini nutritional assessment screening and a visual analogue scale for appetite were assessed.

**Results:** A total of 213 patients were included in the analysis (33% females, median age 59.0 [49.5–67.9] years, 70% overweight/obese upon initial assessment, 73% hospitalised). Sixty-one patients (29% of the total, and 31% of hospitalised patients vs. 21% of patients managed at home,  $p = 0.14$ ) had lost  $>5\%$  of initial body weight (median weight loss 6.5 [5.0–9.0] kg, or 8.1 [6.1–10.9]%). Patients who lost weight had greater systemic inflammation (C-reactive protein 62.9 [29.0–129.5] vs. 48.7 [16.1–96.3] mg/dL;  $p = 0.02$ ), impaired renal function (23.7% vs. 8.7% of patients;  $p = 0.003$ ) and longer disease duration (32 [27–41] vs. 24 [21–30] days;  $p = 0.047$ ) as compared with those who did not lose weight. At multivariate logistic regression analysis, only disease duration independently predicted weight loss (OR 1.05 [1.01–1.10]  $p = 0.022$ ).

**Conclusions:** COVID-19 might negatively impact body weight and nutritional status. In COVID-19 patients, nutritional evaluation, counselling and treatment should be implemented at initial assessment, throughout the course of disease, and after clinical remission.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has spread

rapidly worldwide [1]. COVID-19 patients present primarily with fever, dry cough, and fatigue or myalgia [2]. Clinical manifestations vary widely, ranging from asymptomatic forms to – particularly in older and/or polymorbid patients – acute respiratory distress syndrome (ARDS) requiring hospitalisation, assisted ventilation, and intensive care unit (ICU) admission, with high mortality risk [3]. ICU stay, polymorbidity, and older age are factors that associate with high risk and incidence of malnutrition [4–7]. In patients with severe COVID-19 hyperinflammation with massive release of

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inflammatory cytokines [8,9], as well as use of mechanical ventilation, either non-invasive or invasive, and prolonged hospital stay could further increase the risk of malnutrition.

Patients with mild COVID-19 managed at home might also suffer from malnutrition. Alterations of smell and taste, as well as fatigue and lack of appetite, are reported as very prevalent symptoms in COVID-19 patients [10] that could affect food intake. Confinement at home and COVID-19 symptoms may limit the amount of physical activity, leading to loss of lean mass [11]. These factors, on top of a systemic inflammatory response, might result in malnutrition even in non-hospitalised patients. However, no data are available on the impact of COVID-19 on nutritional status.

We sought to evaluate the incidence of unintentional weight loss and malnutrition in COVID-19 survivors who were either hospitalised or managed at home and re-evaluated after clinical remission.

## 2. Materials and methods

### 2.1. Study design

This was a *post-hoc* analysis of data collected for the COVID-BioB study, a large prospective observational investigation performed at San Raffaele University Hospital, a tertiary health-care hospital in Milan, Italy. The study protocol complies with the Declaration of Helsinki, was approved by the Hospital Ethics Committee (protocol no. 34/int/2020), and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04318366). Full description of patient management and clinical protocols were previously published (16). Signed informed consent was obtained from all patients participating in this study. We included adult (age  $\geq 18$  years) patients with a confirmed diagnosis of COVID-19 who had been discharged home from either a medical ward or the Emergency Department (ED) of San Raffaele University Hospital, and were re-evaluated after remission at the Outpatient COVID-19 Follow-Up Clinic of the same Institution from April 7, 2020, to May 11, 2020 (Supplementary Fig. 1). Confirmed COVID-19 was defined as positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab together with signs, symptoms, and/or radiological findings suggestive of COVID-19 pneumonia. Remission was defined as two negative RT-PCR from a nasal and/or throat swab performed 24 h apart, and no symptoms. Only patients with available anthropometrics (weight and height) recorded upon admission (to the ED or, if not available and only for hospitalised patients, to the medical ward) were included in the analyses. Patients admitted for other reasons and subsequently diagnosed with superimposed SARS-CoV-2 infection were excluded.

### 2.2. Data collection

Data were collected from medical chart review or directly by patient interview and entered in a dedicated electronic case record form (eCRF) specifically developed for the COVID-BioB study. Prior to the analysis, data were cross-checked with medical charts and verified by data managers and clinicians for accuracy. The following variables were collected for all patients: age, sex, body mass index (BMI, calculated as the ratio of weight in kilograms [kg] divided by height in squared metres), PaO<sub>2</sub>/FiO<sub>2</sub> (calculated as the ratio between the arterial partial pressure of oxygen measured on arterial blood gas analysis and the fraction of inspired oxygen), plasma glucose (mg/dL), estimated glomerular filtration rate (eGFR, as estimated by the CKD-EPI equation and expressed as ml/min/1.73 m<sup>2</sup>), haemoglobin, lymphocyte and neutrophil counts ( $\times 10^9/L$ ), lactate dehydrogenase (LDH, U/L), and high-sensitivity C-reactive protein (CRP, mg/dL) on ED admission, peak CRP during

hospital stay, comorbidities (including history of hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, and active cancer) and clinical outcome (discharge from ED or hospital ward, admission to ICU during hospital stay). Measuring weight and height on admission was not feasible due to the workload for nurses and physicians during the peak of the pandemic and the need for contact and airborne precautions in the hospital. Therefore, weight and height on admission were self-reported by patients. Height measured at the follow-up visit was subsequently used to calculate baseline BMI for the present analysis. Disease duration was defined as the time from the diagnosis of SARS-CoV-2 infection by RT-PCR from a nasal and/or throat swab to the time of remission (two negative RT-PCR from a nasal and/or throat swab).

Follow-up outpatient visits were scheduled approximately 3 weeks after discharge, and included a complete internal medicine assessment (collection of medical history, measurement of vital signs, physical examination), and nutritional evaluation (body weight measured to the nearest 0.1 kg using a balance beam scale, height measured to the nearest 0.1 cm using a wall-mounted stadiometer, mini nutritional assessment [MNA] screening and appetite assessment using a visual analogue scale [VAS] ranging from 0 to 100 mm) [12,13]. Weight loss was defined as a reduction  $>5\%$  from initial body weight. At the follow-up visit patients underwent a neurological assessment during which symptoms at disease onset were recorded. Patients were also specifically questioned by the neurologist about whether they had experienced taste and smell disturbances at disease onset.

### 2.3. Statistical analysis

Descriptive statistics were obtained for all study variables. Continuous variables were expressed as medians [25th – 75th percentile]. Categorical variables were summarised as counts and percentages. Fisher exact test or  $\chi^2$  test and Mann–Whitney *U* tests were employed to determine the statistical significance of differences in proportions and medians, respectively. All statistical tests were two-sided. A *p*-value of  $<0.05$  was considered statistically significant. Univariate and multivariate logistic regression analyses were used to estimate adjusted odds ratios (ORs) of weight loss with 95% confidence intervals (CIs) in the whole group and in the subgroup of hospitalised patients. Subgroup analysis was not performed for non-hospitalised patients due to the relatively small number of subjects in this group. Demographic and clinical characteristics potentially associated with weight loss were tested in univariate models. All variables that emerged as predictors ( $p < 0.05$ ) at univariate analysis were used as covariates in the multivariate model. Sex and age were retained in the model regardless of their *p* value at univariate analysis to control for their effect. Missing data were not imputed. Statistical analysis was conducted using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

## 3. Results

A total of 213 patients were included in the present analysis (Supplementary Fig. 1). Approximately one third of patients were females (33.3%), and median age was 59.0 [49.5–67.9] years. Median disease duration, as estimated by the time from diagnosis to negative swab, was 30 [25–38] days. Patient characteristics upon admission to the ED are summarized in Table 1.

Median BMI upon initial admission was 27.1 [24.7–31.0] kg/m<sup>2</sup> with approximately 70% of patients having overweight or obesity. Only four patients (2%) were underweight. Most patients (73%) had been hospitalised and subsequently discharged from a

**Table 1**

Patient characteristics upon admission to the Emergency Department (whole population and comparison between patients managed at home and hospitalised patients).

	All 213	Hospitalised 73.2% (156)	Non-Hospitalised 26.8% (57)	<i>p</i> value	Missing
Age, yrs	59.0 (49.5–67.9)	61 (53–69)	51 (40–60)	<0.001	–
Female, % (n.)	33.3% (71)	28.8% (45)	45.6% (26)	0.022	–
Race, % (n.)					
White	97.7% (208)	98.7% (154)	94.7% (54)	0.010	–
Asian	0.9% (2)	1.3% (2)	0% (0)		
Black	1.4% (3)	0% (0)	5.3% (3)		
Hypertension, % (n.)	36.0% (76)	40.0% (62)	25.0% (14)	0.045	2
Coronary artery disease, % (n.)	6.6% (14)	6.4% (10)	7.1% (4)	1.0	2
Diabetes Mellitus, % (n.)	11.4% (24)	12.9% (20)	7.1% (4)	0.245	2
COPD, % (n.)	2.4% (5)	3.2% (5)	0% (0)	0.328	2
CKD, % (n.)	2.4% (5)	3.2% (5)	0% (0)	0.328	2
Malignancy, % (n.)	1.4% (3)	1.3% (2)	1.8% (1)	1.0	2
BMI, kg/m <sup>2</sup>	27.1 (24.7–31.0)	27.9 (25.1–31.5)	25.7 (24.2–30.4)	0.025	–
BMI category, % (n.)					
Underweight	1.9% (4)	1.9% (3)	1.8% (1)	0.10	–
Normal weight	27.7% (59)	23.1% (36)	40.4% (23)*		
Overweight	40.8% (87)	44.2% (69)	31.6% (18)		
Obesity	29.6% (63)	30.8% (48)	26.3% (15)		
Hypoxemia, % (n.)	38.1% (67)	37.4% (49)	40.0% (18)	0.757	37 <sup>b</sup>
Hypogeusia, % (n.)	43.2% (76)	45.0% (59)	29.8% (17)	0.396	37 <sup>b</sup>
Fever <sup>a</sup> , % (n.)	45.2% (90)	50.0% (72)	32.7% (18)	0.029	14
SpO <sub>2</sub> , %	95 (92–97)	94 (91–96)	97 (96–98)	<0.001	7
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	314 (270–360)	300 (252–333)	377 (342–420)	<0.001	28 <sup>b</sup>
CRP, mg/dl	49.3 (19.9–99.9)	62.4 (31.0–115.2)	14.3 (4.8–46.2)	<0.001	5
LDH, U/L	328 (260–412)	360 (281–430)	256 (211–324)	<0.001	28 <sup>b</sup>
Hb, g/dL	14.1 (12.9–15.2)	14.1 (12.8–15.2)	14.05 (12.3–15.2)	0.82	1
Lym, 10 <sup>9</sup> /L	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.2 (1.0–1.6)	<0.01	15
Neu, 10 <sup>9</sup> /L	4.1 (3.2–6.2)	4.5 (3.5–6.8)	3.5 (2.6–4.4)	<0.001	25 <sup>b</sup>
Plasma glucose (mg/dL)	103 (93–114)	106 (96–117)	98 (87–110)	<0.01	5
AST, U/L	41 (29–56)	44 (32–61)	29 (23–46)	<0.001	2
ALT, U/L	36 (23–54)	38 (23–57)	29 (21–49)	0.059	2
eGFR < 60 mL/min/1.73m <sup>2</sup>	27 (12.9)	25 (16.3)	2 (3.6)	0.015	4

\*Denotes significant difference ( $p < 0.05$ ) vs. the corresponding category in the hospitalised group.Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; BMI, Body Mass Index; SpO<sub>2</sub>, peripheral oxygen saturation; PaO<sub>2</sub>/FiO<sub>2</sub> ratio, ratio between the arterial partial pressure of oxygen measured on arterial blood gas analysis and the fraction of inspired oxygen; CRP, C-Reactive Protein; LDH, lactate dehydrogenase; Hb Haemoglobin; Lym, absolute lymphocyte count; Neu, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate, calculated using the CKD-EPI equation.<sup>a</sup> Tympanic temperature  $\geq 38.0$  °C.<sup>b</sup> Variables with >10% missing values: hypoxemia and hypogeusia (16% and 21.1% missing in the hospitalised and non-hospitalised group, respectively), PaO<sub>2</sub>/FiO<sub>2</sub> ratio (14.7% and 8.8% missing in the hospitalised and non-hospitalised group, respectively), LDH (12.8% and 14.0% missing in the hospitalised and non-hospitalised group, respectively) and absolute neutrophil count (13.5% and 7.0% missing in the hospitalised and non-hospitalised group, respectively). For each categorical variable, percentages were calculated on the number of patients with complete data (valid percentage).

hospital ward. Of these, 5 (3.2%) had been admitted to ICU during the hospital stay. The proportion of males was significantly greater among hospitalised patients ( $\chi^2$ : 5.28,  $p = 0.022$ ), who were also significantly older (Mann–Whitney's U: 6484,  $p < 0.001$ ) and heavier (Mann–Whitney's U: 5.338,  $p = 0.025$ ) than those discharged from the ED and managed at home (Table 1). As expected, hospitalised patients had more severe disease upon presentation (Table 1), being more frequently febrile ( $\chi^2$ : 4.79,  $p = 0.029$ ) and having a worse respiratory function (Mann–Whitney's U: 1345.5 and 688.5 for SpO<sub>2</sub> and PaO<sub>2</sub>/FiO<sub>2</sub> ratio, respectively,  $p < 0.001$  for both) and more altered biochemical markers of disease activity (Mann–Whitney's U: 6733.5, 4952.5, 2874 and 4771.5 for CRP, LDH, absolute lymphocyte and neutrophil counts, respectively,  $p < 0.01$  for all; Table 1). Renal function was also worse in hospitalised patients, with a significantly greater proportion of subjects having CKD stage 3 or worse ( $\chi^2$ : 5.94,  $p = 0.015$ ; Table 1). There were significantly more normal-weight individuals in the group managed at home ( $\chi^2$ : 6.22,  $p = 0.013$ ; Table 1), whereas the proportion of those with overweight/obesity was higher among hospitalised patients ( $\chi^2$ : 5.86,  $p = 0.015$  for overweight/obesity combined). Having overweight/obesity was associated with 2-fold increased risk of being admitted to hospital compared with being under-/normal-weight (odds ratio [OR] 2.18, 95% confidence interval [CI] 1.15–4.13;  $p = 0.017$ ). However, overweight/obesity was

not associated with an increased risk of being admitted to ICU ( $p = 0.997$ ).

Median time from discharge to the follow-up outpatient visit was 23 [23–30] days (26.5 [23.0–33.2] and 22.0 [19.0–28.0] days for hospitalised and non-hospitalised patients, respectively; Mann–Whitney's U: 3311.5,  $p < 0.001$ ). Median length of stay (LoS) for hospitalised patients was 8.0 [5.3–12.0] days. Median BMI at follow-up was 26.3 kg/m<sup>2</sup> [23.56–30.0]. Median percent weight change from initial admission to follow-up was  $-2.3$  [–5.6 – 0.0] % in the whole cohort. Based on the MNA screening tool, one-hundred sixteen (54.7%) and 14 (6.6%) patients were at risk of malnutrition or malnourished, respectively. The proportion of patients hospitalised was significantly greater among those at risk of malnutrition versus those with normal nutritional status (82.8% vs. 61.0%, respectively;  $\chi^2$ : 11.77,  $p = 0.001$ ), but not significantly different from that in malnourished patients (64.3%;  $\chi^2$ : 0.055,  $p = 0.81$ ), likely due to the relatively small number of patients in this category. All patients admitted to ICU were in the group at risk of malnutrition (4.3% of the total).

Sixty-one patients (29% of the total, and 31% of hospitalised patients vs. 21% of patients managed at home,  $\chi^2$ : 2.19,  $p = 0.14$ ) had lost >5% of initial body weight (median weight loss 6.5 [5.0–9.0] kg, or 8.1 [6.1–10.9]%), with a median reduction of 2.3 [1.7–3.2] BMI points. The percentage of patients who lost >10% of initial body

weight was similar between hospitalised and non-hospitalised patients (9.6% vs. 5.3%, Fisher's exact test:  $p = 0.41$ ).

In order to identify factors associated with weight loss, we compared patients who did (WL) or did not (nWL) lose weight. No difference was found between the two groups with respect to age, sex, pre-existing comorbidities and most of the biochemical parameters upon admission (Table 2). CRP levels on admission (Mann–Whitney's U: 5155,  $p = 0.02$ ) were significantly higher in the WL group, where a significantly greater proportion of patients with reduced renal function was also observed ( $\chi^2$ : 8.54,  $p = 0.003$ ; Table 2). Median disease duration was longer in patients who lost weight (Mann–Whitney's U: 5443.5,  $p = 0.047$ , Fig. 1A). Similarly, among hospitalised patients, those who lost weight had a significantly longer LoS (Mann–Whitney's U: 3400,  $p = 0.006$ ; Fig. 1B). No difference was found in appetite VAS scores (55 [41–70] vs. 55 [40–78] mm in patients with or without weight loss, respectively; Mann–Whitney's U: 2059,  $p = 0.89$ ) at the follow-up visit.

At multivariate logistic regression analysis including the whole cohort, only disease duration was identified as an independent predictor of weight loss (OR 1.05 [1.01–1.10]; Wald 5.29,  $p = 0.022$ ) (Supplementary Table 1). At multivariate logistic regression analysis including only hospitalised patients, LoS was the only

independent predictor of weight loss (OR 1.07; CI 95% [1.00–1.13]; Wald 4.57,  $p = 0.03$ ) (Supplementary Table 2).

#### 4. Discussion

This is the first study to assess the impact of COVID-19 on body weight and nutritional status in COVID-19 survivors either managed at home or as inpatients. We found that weight loss and risk of malnutrition were highly prevalent in COVID-19 patients evaluated after clinical remission. Nearly 30% of patients lost more than five per cent of baseline body weight, and more than half were at risk of malnutrition.

It is noteworthy that so many patients, independent of hospitalisation, had a weight loss >5%, i.e. the threshold used to diagnose cancer cachexia [14]. As suggested by the European Society of Enteral and Parenteral Nutrition (ESPEN), prevention, diagnosis and treatment of malnutrition should be considered in the management of COVID-19 patients to improve both short- and long-term prognosis [8]. However, the few studies available so far have focused on hospitalised patients and selected populations, such as elderly or critically ill patients [15,16]. Our study expands the knowledge of the impact of COVID-19 on nutritional status to a

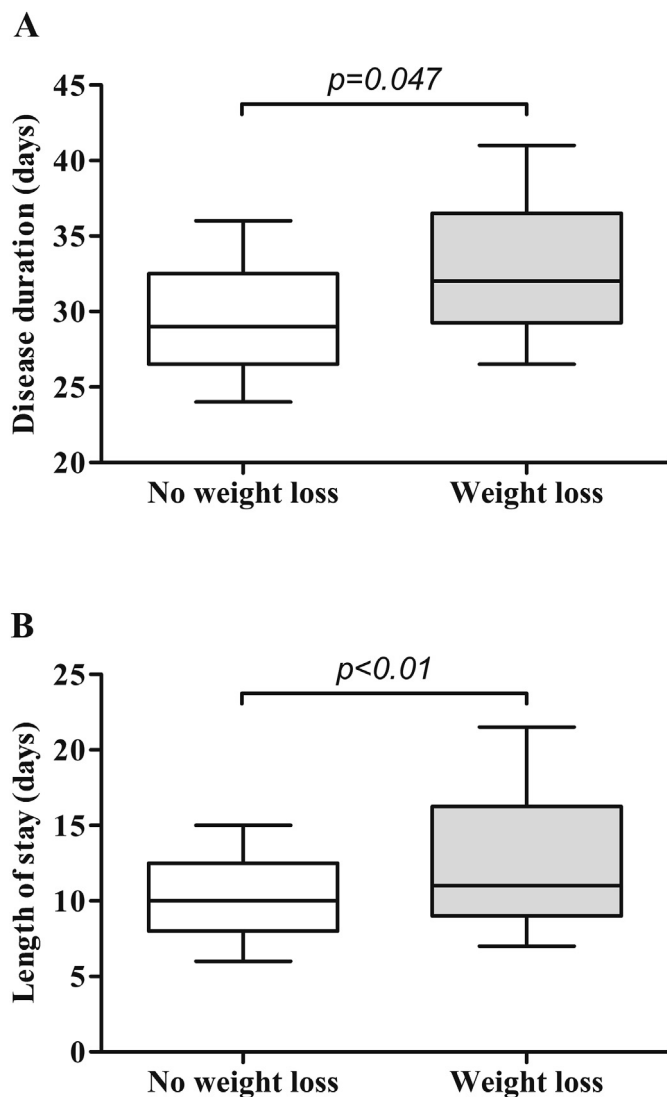
**Table 2**  
Comparison between patients with or without weight loss.

	Weight loss 28.6% (61)	No weight loss 71.4% (152)	<i>p</i> value	Missing
Age, yrs	59.7 (51.0–69.0)	57.5 (49.0–67.0)	0.66	–
Female, % (n.)	34.4% (21)	32.9% (50)	0.83	–
Race, % (n.)				
White	100% (61)	96.7% (147)	0.18	–
Asian	0% (0)	1.3% (2)		
Black	0% (0)	2.0% (3)		
Hypertension, % (n.)	36.7% (22)	35.8% (54)	0.90	2
Coronary artery disease, % (n.)	10.0% (6)	5.3% (8)	0.22	2
Diabetes mellitus, % (n.)	10.0% (6)	11.9% (18)	0.69	2
COPD, % (n.)	3.3% (2)	2.0% (3)	0.62	2
CKD, % (n.)	5.0% (3)	1.4% (2)	0.14	2
Malignancy, % (n.)	1.7% (1)	1.3% (2)	1.0	2
BMI, kg/m <sup>2</sup>	27.5 (25.6–32.2)	27.1 (24.3–30.4)	0.207	–
BMI category, % (n.)				
Underweight	0% (0)	2.6% (4)	0.18	–
Normal weight	21.3% (13)	30.3% (46)		
Overweight	47.5% (29)	38.2% (58)		
Obesity	31.1% (19)	28.9% (44)		
Hyposmia, % (n.)	40.4% (21)	37.1% (46)	0.68	37 <sup>b</sup>
Hypogeusia, % (n.)	46.2% (24)	41.9% (52)	0.60	37 <sup>b</sup>
Fever <sup>a</sup> , % (n.)	41.8% (23)	46.5% (67)	0.55	14
SpO <sub>2</sub> , %	95 (91–96)	95 (93–97)	0.09	7
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	307 (273–347)	324 (265–367)	0.56	28 <sup>b</sup>
CRP, mg/dl	62.9 (29.0–129.5)	48.7 (16.1–96.3)	0.02	5
Peak CRP, mg/dL	104.2 (57.0–184.6)	62.9 (41.3–144.5)	0.05	6
LDH, U/L	340 (275–459)	325 (254–401)	0.16	28 <sup>b</sup>
Hb, g/dL	14.0 (12.7–15.3)	14.2 (13.0–15.2)	0.47	1
Lym, 10 <sup>9</sup> /L	0.7 (1.0–1.3)	0.8 (1.0–1.3)	0.71	15
Neu, 10 <sup>9</sup> /L	4.5 (3.4–7.1)	3.9 (2.9–6.0)	0.09	25
Plasma glucose (mg/dL)	104 (91–124)	103 (94–113)	0.501	5
AST, U/L	43 (30–64)	39 (28–55)	0.34	2
ALT, U/L	39 (23–57)	34 (23–53)	0.49	2
eGFR < 60 mL/min/1.73m <sup>2</sup>	14 (23.7)	13 (8.7)	0.003	4
Hospitalisation, % (n.)	80.3% (49)	70.4% (107)	0.139	–
ICU, % (n.)	8.2% (5)	–	–	–

Abbreviations: COPD Chronic Obstructive Pulmonary Disease; CKD Chronic Kidney Disease; BMI, Body Mass Index; SpO<sub>2</sub> peripheral oxygen saturation; PaO<sub>2</sub>/FiO<sub>2</sub> ratio: ratio between the arterial partial pressure of oxygen measured on arterial blood gas analysis and the fraction of inspired oxygen; CRP, C-Reactive Protein; LDH, lactate dehydrogenase; Hb Haemoglobin; Lym, absolute lymphocyte count; Neu, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR estimated glomerular filtration rate, calculated using the CKD-EPI equation; ICU, intensive care unit.

<sup>a</sup> Tympanic temperature  $\geq 38.0$  °C.

<sup>b</sup> Variables with >10% missing values: hyposmia and hypogeusia (14.8% and 18.4% missing in patients with or without weight loss, respectively), PaO<sub>2</sub>/FiO<sub>2</sub> ratio (18.0% and 11.2% missing in patients with or without weight loss, respectively), LDH (16.4% and 11.8% missing in patients with or without weight loss, respectively) and absolute neutrophil count (9.8% and 12.5% missing in patients with or without weight loss, respectively). For each categorical variable, percentages were calculated on the number of patients with complete data (valid percentage).



**Fig. 1.** Disease duration (as estimated by the time from diagnosis to negative swab, all patients [A]) and length of stay (hospitalised patients [B]) in patients who did not lose weight and those who lost weight.

broader population, with a wide range of ages and disease severity, spanning from patients with mild disease managed at home to inpatients with severe disease admitted to the ICU. We searched the literature for data on weight loss and malnutrition in similar diseases (i.e. Middle East respiratory syndrome [MERS] and SARS), but could not find any published data for comparison with our findings. Most published data on the effects of acute diseases on nutritional status relate to critically ill patients. The inflammatory nature of COVID-19 and the global spread of the disease provide a unique opportunity to study the effects of acute inflammatory illness of a wide range of severity on body weight and nutritional status.

Several mechanisms may contribute to weight loss and malnutrition in COVID-19 patients. When comparing patients with or without weight loss, we found that those who lost weight had greater systemic inflammation (baseline CRP and, in hospitalised patients, peak CRP values), worse renal function (proportion of patients with an eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>), and longer disease duration. Acute systemic inflammation deeply affects several metabolic [17] and hypothalamic [18] pathways contributing to anorexia and decreased food intake as well as elevation of resting expenditure and increased muscle catabolism [19]. Of note,

acute inflammatory events can trigger persistent neuro-inflammatory responses in vulnerable individuals, which may perpetuate inflammation and wasting even after the acute phase [18,20]. Impaired renal function is an important risk factor for malnutrition, the prevalence of protein-energy wasting increasing with declining eGFR [21]. At multivariate analyses only disease duration and - in hospitalised patients - length of stay were significant independent predictors of weight loss, reflecting the importance of disease severity and inflammation to weight loss. In our cohort of COVID-19 patients, weight loss occurred in a relatively short time (median disease duration: 32 [27–41] days). This is consistent with previous studies showing that even short periods of bed rest induce marked reductions in muscle protein synthesis resulting in loss of skeletal muscle mass, both in middle-aged and elderly individuals [22–24]. Furthermore, malnutrition is strongly associated with loss of muscle mass and strength in both community-dwelling and hospitalised individuals [25]. Although we did not measure body composition, it is likely that the weight loss observed in our cohort of COVID-19 patients was, at least in part, due to loss of lean body mass caused by bed rest or muscle disuse, both in hospitalised and non-hospitalised patients. This could negatively impact time to full recovery and patients' health status. It has been reported that patients with ARDS exhibit an important weight loss at hospital discharge, approximately 18% of their baseline body weight, mainly due to lean body mass loss [26]. Regain of body weight in the following year is mainly due to an increase in fat mass [27], which may bear negative implications for cardiovascular risk and functional status. These might be particularly relevant to COVID-19 patients, given the high prevalence of overweight and obesity reported here and in other studies [28,29]. Our findings support an association between obesity and risk of hospital admission [30] but challenge the association between BMI and critical illness, consistent with recent data on patients hospitalised with COVID-19 in New York City [29]. Previous studies demonstrated that obesity is associated with increased risk of ARDS, but lower risk of mortality [31]. This "obesity paradox" has also been observed in patients with obesity hospitalised for pneumonia in a non-ICU setting [32]. Pre-conditioning induced by the low-grade chronic inflammation associated with obesity has been postulated as a protective mechanism against further insults to the lungs [33]. Increased availability of nutritional reserves protecting obese subjects against hypercatabolism is another possible explanation. This hypothesis is supported by the observation that early enteral nutrition in the ICU minimises or even abolishes the survival disadvantage for under- and normal-weight patients as compared with those in higher BMI categories [34] and by the finding that recent weight loss has a negative impact on mortality even in non-critically ill overweight and obese inpatients [35]. This suggests that weight loss should not be allowed in the hospital setting, even in patients with obesity. The fact that patients with overweight/obesity lost a significant amount of weight and developed or were at risk for malnutrition supports the ESPEN recommendation that individuals with obesity should be screened for malnutrition and receive nutritional counselling, as malnutrition is defined not only by low body mass but also by unhealthy body composition and skeletal muscle mass [8]. Sarcopenic obesity, i.e. the coexistence of excess fat mass and sarcopenia, is a prevalent and often underrecognized complication of obesity that may associate with worse clinical outcomes [36].

Other factors that were not specifically assessed but may have contributed to weight loss and risk of malnutrition in our cohort are medical treatments and mechanical ventilation in hospitalised patients [37,38]. Emotions such as fear and sadness may reduce the desire or motivation to eat [39]. In patients managed at home, confinement may limit the access to food and/or the variety of food

choices [40] which, as in a vicious cycle, is a source of frustration, anxiety and anger [41], besides having direct implications for nutrition. Surprisingly, we found no association between alterations in smell and taste, which are known to increase malnutrition risk in cancer patients [42] and are highly prevalent in COVID-19 [10].

Finally, it is noteworthy that patients who lost weight in our cohort had not yet returned at the initial body weight at the follow-up visit (a median of 23 [23–30] days since discharge). This highlights the need for nutritional evaluation and counselling/intervention not only at diagnosis or for hospitalised patients, but also for those managed at home and at follow-up, with a careful reassessment to monitor weight changes and nutritional status.

Our findings should be interpreted in light of the limits of the study design. Patients evaluated in our study were COVID-19 survivors. We did not include patients with worse outcomes, i.e. those who died or were still hospitalised. It is plausible that the incidence and prevalence of weight loss and the risk of malnutrition among COVID-19 patients are even greater than reported here, reflecting a heavier nutritional burden. Further limits of our study are the *post-hoc* nature of our analysis and the use of patient-reported weight upon admission. Large cohort studies suggest that self-reported weight is slightly underestimated [43,44]. It is possible that we underestimated baseline BMI and the amount of weight lost. We did not assess body weight at hospital discharge nor body composition. During a time of unprecedented workload for healthcare professionals, and given the restrictions imposed by the need of isolating patients to prevent viral spread, the assessment of body weight and body composition was unfeasible. For the same reason, some baseline data were not recorded and were missing for the analyses. Information on taste and/or smell disturbances was missing for 17.4% of patients because the neurological assessment during which these symptoms were investigated was introduced one week after the beginning of the outpatient follow-up clinic. Nearly all patients with taste and/or smell disturbances at COVID-19 onset reported full recovery of symptoms, but this information was not systematically recorded. A further limitation is the lack of repeat biochemical assessment at the follow-up visit. This is because the follow-up evaluation at our Institution comprises a general medical assessment including anthropometric measurements and the MNA screening. Patients with specific needs are referred to nutrition professionals for further assessment, and laboratory testing is requested based on individual clinical needs. At this time, we were not able to assess the recovery rate of nutritional status in COVID-19 survivors. Some patients reported partial regain of lost weight prior to the clinic visit, but most of them were unable to provide detailed information on weight changes. These data were not sufficient nor reliable for inclusion in the analysis. The main scope of this first study was to describe the incidence of unintentional weight loss and malnutrition in COVID-19 survivors. Subsequent assessments of body weight and nutritional status including biochemical parameters will help fill this research gap. Further questions that remain open are • what nutritional screening strategies should be implemented for patients managed at home? • what kind of nutritional support/counselling should be provided in the outpatient and inpatient setting, and for the transition phase? • what are the consequences of COVID-19-associated weight loss on patient recovery? • what are the effects of COVID-19-associated weight loss on body composition?

In conclusion, we report, for the first time to our knowledge, a very high incidence of weight loss and risk of malnutrition among COVID-19 survivors, independent of hospitalisation. The association of unintentional weight loss with worse clinical outcomes has long been recognised [45–47]. Implementing nutritional management strategies is crucial for hospitalised patients, particularly

those in the ICU or with older age and polymorbidity [8,48]. However, our findings support the notion that even individuals managing or recovering from COVID-19 symptoms at home should receive counselling on how to maintain an adequate intake of calories, protein, and fluids [49]. Strategies such as using remote nutritional screening tools recently developed for primary practise [50] should be implemented to improve the nutritional management of patients managed at home.

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## Statement of authorship

Conceptualization: LDF, CC, PRQ; Data curation: LDF, RDL, MDA, VS, CC; Formal analysis: LDF, CC; Investigation: LDF, RDL, CC; Methodology: LDF, CC, PRQ; Project administration: CC; Supervision: CC; Validation: RM, AS, PRQ, CC; Visualization: LDF, RDL, MDA, VS, RM, AS, PRQ, CC; Writing - original draft: LDF, CC; Writing - review & editing: LDF, RDL, MDA, VS, RM, AS, PRQ, CC.

## Conflict of interest

The authors have no competing interests to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2020.10.043>.

## References

- [1] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382:1199–207.
- [2] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
- [3] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020.
- [4] Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. *Clin Nutr* 2018;37:336–53.
- [5] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr* 2019;38:48–79.
- [6] Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Goisser S, Hooper L, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. *Clin Nutr* 2019;38:10–47.
- [7] World Health Organization. Novel coronavirus(2019-nCoV) situation report - 11. Available at: [https://www.who.int/docs/default-source/coronavirus/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7\\_4](https://www.who.int/docs/default-source/coronavirus/situation-reports/20200131-sitrep-11-ncov.pdf?sfvrsn=de7c0f7_4). [Accessed 6 April 2020].
- [8] Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr* 2020;39:1631–8.
- [9] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4.
- [10] Lechien JR, Chiesa-Estomba CM, De Siaty DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020;277:2251–61.
- [11] Briguglio M, Pregliasco FE, Lombardi G, Perazzo P, Banfi G. The malnutritional status of the host as a virulence factor for new coronavirus SARS-CoV-2. *Front Med (Lausanne)* 2020;7:146.
- [12] Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord* 2000;24:38–48.

- [13] Rubenstein LZ, Harker JO, Salva A, Guigoz Y, Vellas B. Screening for under-nutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;56:M366–72.
- [14] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;12:489–95.
- [15] Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, et al. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. *Eur J Clin Nutr* 2020;74:871–5.
- [16] Zhang P, He Z, Yu G, Peng D, Feng Y, Ling J, et al. The modified NUTRIC score can be used for nutritional risk assessment as well as prognosis prediction in critically ill COVID-19 patients. *Clin Nutr* 2021;40(2):534–41.
- [17] Varela ML, Mogildea M, Moreno I, Lopes A. Acute inflammation and metabolism. *Inflammation* 2018;41:1115–27.
- [18] Burfeind KG, Michaelis KA, Marks DL. The central role of hypothalamic inflammation in the acute illness response and cachexia. *Semin Cell Dev Biol* 2016;54:42–52.
- [19] Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. *Clin Nutr* 2019;38:1–9.
- [20] Hawkins RB, Raymond SL, Stortz JA, Horiguchi H, Brakenridge SC, Gardner A, et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. *Front Immunol* 2018;9:1511.
- [21] Lodebo BT, Shah A, Kopple JD. Is it important to prevent and treat protein-energy wasting in chronic kidney disease and chronic dialysis patients? *J Ren Nutr* 2018;28:369–79.
- [22] Arentson-Lantz EJ, English KL, Paddon-Jones D, Fry CS. Fourteen days of bed rest induces a decline in satellite cell content and robust atrophy of skeletal muscle fibers in middle-aged adults. *J Appl Physiol* (1985) 2016;120:965–75.
- [23] English KL, Mettler JA, Ellison JB, Mamerow MM, Arentson-Lantz E, Patarini JM, et al. Leucine partially protects muscle mass and function during bed rest in middle-aged adults. *Am J Clin Nutr* 2016;103:465–73.
- [24] Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. *JAMA* 2007;297:1772–4.
- [25] Landi F, Camprubi-Robles M, Bear DE, Cederholm T, Malafarina V, Welch AA, et al. Muscle loss: the new malnutrition challenge in clinical practice. *Clin Nutr* 2019;38:2113–20.
- [26] Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saïdi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–93.
- [27] Chan KS, Mourtzakis M, Aronson Friedman L, Dinglas VD, Hough CL, Ely EW, et al. Evaluating muscle mass in survivors of acute respiratory distress syndrome: a 1-year multicenter longitudinal study. *Crit Care Med* 2018;46:1238–46.
- [28] Caussy C, Pattou F, Wallet F, Simon C, Chalopin S, Telliam C, et al. Prevalence of obesity among adult inpatients with COVID-19 in France. *Lancet Diabetes Endocrinol* 2020;8:562–4.
- [29] Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020;395:1763–70.
- [30] Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 Years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis* 2020;71:896–7.
- [31] Zhi G, Xin W, Ying W, Guohong X, Shuying L. "Obesity paradox" in acute respiratory distress syndrome: asystematic review and meta-analysis. *PLoS One* 2016;11:e0163677.
- [32] Atamna A, Elis A, Gilady E, Gitter-Azulay L, Bishara J. How obesity impacts outcomes of infectious diseases. *Eur J Clin Microbiol Infect Dis* 2017;36:585–91.
- [33] Ball L, Serpa Neto A, Pelosi P. Obesity and survival in critically ill patients with acute respiratory distress syndrome: a paradox within the paradox. *Crit Care* 2017;21:114.
- [34] Harris K, Zhou J, Liu X, Hassan E, Badawi O. The obesity paradox is not observed in critically ill patients on early enteral nutrition. *Crit Care Med* 2017;45:828–34.
- [35] Barazzoni R, Sulz I, Schindler K, Bischoff SC, Gortan Cappellari G, Hiesmayr M, et al. A negative impact of recent weight loss on in-hospital mortality is not modified by overweight and obesity. *Clin Nutr* 2020;39:2510–6.
- [36] Donini LM, Busetto L, Bauer JM, Bischoff S, Boirie Y, Cederholm T, et al. Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review. *Clin Nutr* 2020;39:2368–88.
- [37] Campbell IT. Limitations of nutrient intake. The effect of stressors: trauma, sepsis and multiple organ failure. *Eur J Clin Nutr* 1999;53(Suppl 1):S143–7.
- [38] Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;29:154–9.
- [39] Macht M. Characteristics of eating in anger, fear, sadness and joy. *Appetite* 1999;33:129–39.
- [40] Naja F, Hamadeh R. Nutrition amid the COVID-19 pandemic: a multi-level framework for action. *Eur J Clin Nutr* 2020.
- [41] Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 2020;395:912–20.
- [42] Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: a systematic review. *J Cancer Surviv* 2018;12:479–94.
- [43] Flegal KM, Ogden CL, Fryar C, Afful J, Klein R, Huang DT. Comparisons of self-reported and measured height and weight, BMI, and obesity prevalence from national surveys: 1999–2016. *Obesity (Silver Spring)* 2019;27:1711–9.
- [44] Hodge JM, Shah R, McCullough ML, Gapstur SM, Patel AV. Validation of self-reported height and weight in a large, nationwide cohort of U.S. adults. *PLoS One* 2020;15:e0231229.
- [45] Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev* 2009;22:93–108.
- [46] Myers J, Lata K, Chowdhury S, McAuley P, Jain N, Froelicher V. The obesity paradox and weight loss. *Am J Med* 2011;124:924–30.
- [47] Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, et al. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. *Mayo Clin Proc* 2014;89:1368–77.
- [48] Puig-Domingo M, Marazuela M, Giustina A. COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. *Endocrine* 2020;68:2–5.
- [49] Handu D, Moloney L, Rozga M, Cheng F. Malnutrition care during the COVID-19 pandemic: considerations for registered dietitian nutritionists evidence analysis center. *J Acad Nutr Diet* 2020.
- [50] Krznaric Z, Bender DV, Laviano A, Cuerda C, Landi F, Monteiro R, et al. A simple remote nutritional screening tool and practical guidance for nutritional care in primary practice during the COVID-19 pandemic. *Clin Nutr* 2020;39:1983–7.