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The link between nutritional status and outcomes in COVID-19 patients in ICU: Is obesity or sarcopenia the real problem?

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Obesity is frequent among COVID-19 patients and data indicate that this condition is associated with poor outcomes [1]. Nutritional status, in particular in COVID-19 patients in intensive care unit (ICU), was often assessed by the calculation of body mass index (BMI) classes, allowing to indicate the presence/absence of overweight or obesity [2]. However, scanty information is available on body composition in COVID-19 patients in ICU [2] and, more importantly, on patient's muscularity. In fact, most of the studies conducted in these patients indicate a high prevalence of increased adiposity (based on high visceral adipose tissue by computed tomography - CT) that seems to be able to predict the severity of the disease [3,4]. Obesity was shown to predict COVID-19 severity also among young patients [5].

In ICU (not COVID-19 patients), recent evidences showed that low skeletal muscle mass as assessed by CT, was a risk factor for reduced survival in mechanically ventilated patients, revealing that BMI was not an independent predictor of mortality when muscularity was considered [6].

In addition, low Skeletal Muscle Area (SMA) and low skeletal muscle radiodensity, indicating loss of muscle quality, were associated with increased infections in non-COVID-19 patients in ICU [7].

Therefore, by the present exploratory study we aimed to describe,in ICU COVID-19 patients the status of muscularity, assessing SMA and skeletal muscle index (SMI), and its association(s) with complications and mortality during the ICU stay.

Patients enrollment, clinical parameters and outcomes

We enrolled critical patients with a diagnosis of COVID-19 performed by nasopharyngeal or oropharyngeal swab (positive real-time reverse-transcriptase polymerase chain reaction - RT-PCR) and byCTscan admitted in the ICU of Sant'Andrea Hospital, Sapienza University of Rome, Italy in the period between March and May 2020. The local ethics committee approved the study and decided that consent could be waived in the context of the pandemic.

We recorded clinical characteristics, including comorbidities and laboratory findings at admission. We also collected data about complications, including acute kidney injury, bleedings and thromboembolic events (pulmonary embolism, acute myocardial infarction, line clotted, deep venous thrombosis), as well as mortality during the ICU hospitalization. All the patients received the same standard therapy according to Italian recommendation (www.aifa.gov.it).

Nutritional status and muscularity assessment

We collected data about anthropometry, including waist and arm circumference, body mass index (kg/m^2). We assessed the presence of metabolic syndrome according to the criteria of International Diabetes Federation (2006).

For each patient, by CT images we obtained axial slices at the level of the third lumbar vertebrae (L3) and we estimated the SMA (cm^2), which includes psoas, paraspinal and abdominal wall muscles. The SMI (cm^2/m^2) was calculated dividing SMA (cm^2) by height of the patient expressed in m^2. All the CT images were analyzed in a separate workstation, using Osirix Lite DICOM Viewer (version 11.0.3, Geneva, Switzerland).

Patients characteristics were shown as mean ± standard deviation and median with 25th and 75th percentiles for continuous normally and non-normally distributed variables. Categorical variables were described as number (%). To analyze differences between groups we used the two-tailed t-test or Mann-Whitney according to normal or non-normal distribution. Also, to compare patients with lower vs higher muscle mass, we used as cutoff values the sex-specific median of SMA and SMI.

Pearson's chi-square test was used to establish association between categorical variables. A p-value < 0.05 was considered statistically significant.

Patient's characteristics

We collected data from 25 patients (56% male) with a confirmed diagnosis of COVID-19 presenting with a median age of 67 years (IQR 60; 78). The mean BMI (kg/m^2) was 28.8 ± 4.8 and the prevalence of overweight and obesity was 44% (11/25) and 32% (8/25), respectively. None of the patients presented with a BMI below 18.5. The prevalence of

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metabolic syndrome was 56% (14/25).

The most common comorbidities were hypertension (52%), diabetes (16%) and chronic kidney disease (8%) (Table 1).

Fourteen out of 25 patients (56%) had at least 1 comorbidity and 5 patients (20%) had 2 or more comorbidities. Clinical characteristics of the participants are summarized in Table 1.

Indices of muscularity

We assessed muscle mass in 24 out of 25 patients because in one patient the CT scan images presented insufficient quality for the analyses.

The median SMA (cm^2) was 71 (IQR 61.75; 77.25), whereas the SMI median value (cm^2/m^2) was 24.86 (IQR 23.36; 25.69).

No differences in terms of SMA and SMI were observed between males (median SMA 73.5; median SMI 24.5) and females (median SMA 67.5; median SMI 25.3 ($p = 0.197$; $p = 0.542$, respectively). Moreover, for both muscle measurements, we did not find difference between overweight/obese patients (median SMA 70.5; median SMI 25.31) compared to those with normal BMI (median SMA 73; median SMI 24.3) ($p = 0.912$; $p = 0.416$, respectively), as well as between patients with or without metabolic syndrome ($p = 0.099$; $p = 0.646$, respectively) or between those with one vs those with two or more comorbidities ($p = 0.952$; $p = 0.818$, respectively). No correlation was found between age and both SMA ($p = 0.48$) and SMI ($p = 0.24$).

Based on previous cutoffs in critical care for low muscle mass – SMA (cm^2) (110 for females and 170 for males) [6] and SMI (cm^2/m^2) (42.0, independently by sex) [8], all the patients of our cohort (100%) could be classified as sarcopenic.

Association between complications, mortality and indices of muscularity

The median duration of the ICU stay was 12 days (IQR 5; 26). The complications observed were thromboembolic events in 6 out of 25 (24%), bleedings in 4 out of 25 (16%) and acute kidney injury in 5 out of 25 (20%).

The number and type of complications were not associated with the presence of overweight (BMI 25–29.9) and/or obesity (BMI $\geq$ 30).

Considering the small number of participants, to verify differences in terms of complications according to lower muscularity vs higher muscularity, we used the SMA and SMI sex-specific median values.

Patients presenting with these two muscle measurements below the median (SMA below 67.5 for females and 73.5 for males and SMI below 25.31 for females and 24.46 for males) showed one or more complications more frequently than those with SMA and SMI values over the median ($p = 0.04$). Seven out of 25 patients died (28%) during the hospitalization. No differences were found in terms of SMA, SMI and BMI classes between survivors and non-survivors (Table 1).

No association was present between low muscularity (SMA and SMI below the sex-specific median) and the number of deaths.

Discussion

Our study confirmed, in a small cohort of COVID-19 patients in ICU, a high prevalence of overweight and obesity, as well as a high percentage of individuals affected by metabolic syndrome (more than 50%). Moreover, in line with previous larger evidences [9], the most common comorbidity in our cohort was represented by essential hypertension. It has been well established that nutritional status represents

Table 1
Patient's characteristics

Parameter	Total Participants (*n* = *25*)	Low muscularity*(*n* = *12*)	High muscularity*(*n* = *12*)	§p-value	Survivors (*n* = *18*)	Non-Survivors (*n* = *7*)	#p-value
Age, y	67 (60; 78)	67 (58; 71)	67 (62; 78)	0.422	64 (59; 68)	78 (70; 79.5)	0.034
Male, (%)	14 (56)	7 (58)	7 (58)	>0.99	9 (50)	5 (71)	0.332
Hemoglobin, g/dL	12.9 ± 2.0	12.3 ± 2.2	13.5 ± 1.7	0.138	12.5 ± 2.2	14.0 ± 0.7	0.081
White blood cell count, /μL	9590 ± 4854	9955 ± 4269	8625 ± 5224	0.502	8462 ± 4164	12492 ± 5609	0.061
Lymphocyte count, /μL	720 (550; 1130)	740 (430; 1200)	710 (595; 1110)	0.760	695 (467.5; 890)	1200 (720; 1410)	0.174
Neutrophil count, /μL	8066 ± 4670	8980 (6725; 10600)	5890 (4870; 7538)	0.215	7063 ± 3563	10643 ± 6364	0.085
Neutrophil-Lymphocyte Ratio	8.52 (5.25; 16.02)	11.65 (5.45; 17.34)	6.22 (5.06; 11.18)	0.401	9.34 (5.55; 14.33)	5.79 (4.86; 19.19)	0.976
Albumin, g/dL	3.2 ± 0.5	3.2 ± 0.4	3.3 ± 0.6	0.479	3.2 ± 0.5	3.3 ± 0.6	0.667
CRP, mg/dl	15.6 (9.4; 19.2)	15.3 (12.4; 19.3)	14.8 (8.9; 19.8)	0.841	18.1 (11.6; 19.5)	12.3 (7.4; 16.8)	0.263
Orotracheal Intubation, (%)	15 (60)	7 (58)	7 (58)	>0.99	8 (44)	7 (100)	0.020
Anthropometric and body composition indices							
BMI, kg/m^2	28.8 ± 4.8	29.4 ± 5.7	28.3 ± 4.0	0.589	28.98 ± 5.47	28.20 ± 2.75	0.724
BMI ≥ 25, (%)	19 (76)	8 (67)	10 (83)	0.346	12 (67)	7 (100)	0.137
BMI 18.5–24.9, (%)	6 (24)	4 (33)	2 (17)	0.346	6 (33)	0 (0)	0.137
Waist circumference, cm	113 ± 23	117 ± 26	112 ± 21	0.603	117 ± 25	103 ± 13	0.191
Arm circumference, cm	31 ± 4	31 ± 3	31 ± 4	0.913	31 ± 4	31 ± 3	0.808
SMA, cm^2	71 (61.75; 77.25)	62 (54; 71)	78 (71; 98)	0.001	71 (62.5; 76.25)	72.5 (64.25; 77)	0.741
SMI, cm^2/m^2	24.86 (23.36; 25.69)	22.99 (20.44; 24.12)	25.78 (25.35; 33.81)	<0.0001	25 (22.63; 25.4)	25 (24.08; 25.86)	0.667
Comorbidities							
Hypertension, (%)	13 (52)	7 (58)	5 (42)	0.414	8 (44)	5 (71)	0.225
Diabetes, (%)	4 (16)	2 (17)	2 (17)	>0.99	3 (17)	1 (14)	0.884
Chronic kidney disease, (%)	2 (8)	1 (8)	1 (8)	>0.99	1 (6)	1 (14)	0.470
Complications							
Acute kidney injury, %	5 (20)	2 (17)	2 (17)	>0.99	0 (0)	5 (71)	0.0004
Embolic events, %	6 (24)	5 (71)	1 (8)	0.059	3 (17)	3 (43)	0.169
Bleedings, %	4 (16)	4 (33)	0 (0)	0.271	3 (17)	1 (14)	0.884

Abbreviations. CRP, C-reactive protein; BMI, body mass index; SMA, skeletal muscle area, SMI, skeletal muscle index

Data are shown as mean ± standard deviation and median (interquartile range) for nonnormally distributed variables.

* Musculerity (SMI) available in 24 out of 25 patients

§ patients with low muscularity (below the sex-specific median value of SMI) vs patients with high muscularity (over the sex-specific median value of SMI)

survivors vs non-survivors.

a clinically relevant aspect to be assessed in ICU to stratify the risk of complications and mortality, independently by other factors including BMI and sex [6]. In addition, in critical care, as well as in chronic diseases (e.g. cancer, chronic kidney disease, cirrhosis, etc.), body weight and BMI appear not accurate to reflect nutritional status [6], in particular in small cohorts of patients such as ours. In this light, body composition analysis adds important information, specifically regarding low muscle mass assessed by CT, known to be a negative predictor of survival in ICU [8].

Our data showed that SMA and SMI, both indices of muscularity, were low when compared to the available data obtained among healthy individuals and more importantly in critically ill patients [6,8]. Our results indicate that these indices were not different between patients with normal BMI vs those with higher BMI ($\geq$ 25) and between males and females. Also, considering the emergency setting of the COVID-19 pandemic and therefore the limited clinical information obtained by the relatives, we did not have information regarding patient's unintentional body weight loss, which is a well-known factor related to low muscle mass and higher in-hospital mortality [10].

Unfortunately, due to the small number of participants we did not have the power to detect an association between low muscularity and death. However, we were able to find an association between low muscle mass (defined with SMI and SMA values below the sex-specific median) and the presence of at least one complication during ICU stay. This observation appears a novel one, suggesting the importance of changes in nutritional status and body composition (muscle mass), beyond BMI, and outcomes in critically COVID-19 patients.

Our study has several limitations including the small number of COVID-19 cases, the lack of a control group (non-COVID-19 critically ill patients) and the absence of an analysis of the changes of muscle mass overtime, although our aim was to assess muscularity in a cross-sectional setting. We did not assess adiposity which may have added information regarding outcomes.

In conclusion, our study although exploratory, suggests the importance of the evaluation of muscle mass in COVID-19 patients in ICU to better stratify the risk of complications, and likely mortality, and to implement nutritional strategies in this setting. Larger trials are mandatory to confirm our initial results.

Author Contributions

AM and DA were responsible for the development of the research. AM, GI performed statistical analyses and contributed to the interpretation of the findings. AM wrote the paper. VR, CC performed images analysis. DA and MR collected the data. MM contributed to the manuscript revision and interpretation of the data.

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Declaration of Competing Interests

The authors declare no conflict of interest.

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