Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

The impact of body composition on mortality of COVID-19 hospitalized patients: A prospective study on abdominal fat, obesity paradox and sarcopenia

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SUMMARY

Background & aims: Obesity has been described as a predisposing risk factor to severe forms of COVID-19, but conflicting results are emerging on its real impact on the mortality of COVID-19. We aimed to compare clinical outcomes and mortality among COVID-19 patients according to obesity, metabolic syndrome and adiposity distribution.

Methods: We conducted a prospective observational study of all consecutive adult patients with a confirmed diagnosis of SARS-CoV-2 infection admitted to the Infectious Diseases Clinic at Udine Hospital, Italy, from January 2021 to February 2021. At admission, the study population was submitted to specific anthropometric, laboratory and bioimpedance analysis (BIA) measurements and divided into five groups according to: 1) BMI < or >30 kg/m^2; 2) waist circumference (WC) < or >98 cm for women, < or >102 cm for men; 3) presence or absence of metabolic syndrome (MS); 4) visceral adipose tissue (VAT) distribution; and 5) presence or absence of sarcopenia (SP) both based on BIA. We then compared clinical outcomes (ventilatory support, intensive care unit (ICU) admission, ICU length of stay, total hospital length of stay and mortality), immune and inflammatory makers and infectious and non-infectious acute complications within the five groups.

Results: A total of 195 patients were enrolled in the study. The mean age of patients was 71 years (IQR 61–80) and 64.6% (126) were male. The most common comorbidities were hypertension (55.9%) and MS (55.4%). Overall mortality was 19.5%. Abdominal adiposity, measured both with WC and with BIA, and SP were significantly associated with need for increased ventilator support ($p = 0.013$ for WC; $p = 0.037$, 0.027 and 0.009 for VAT; $p = 0.004$ and 0.036 for FMI; and $p = 0.051$ for SP), but not with ICU admission (WC $p = 0.627$, VAT $p = 0.153$, FMI $p = 0.519$ and SP $p = 0.938$), length of stay (WC $p = 0.345$, VAT $p = 0.650$, FMI $p = 0.159$ and SP $p = 0.992$) and mortality (WC $p = 0.277$, VAT $p = 0.533$, FMI $p = 0.957$ and SP $p = 0.211$). Obesity and MS did not discriminate for the intensity of ventilatory outcome ($p = 0.142$ and $p = 0.198$, respectively), ICU admission ($p = 0.802$ and $p = 0.947$, respectively), length of stay ($p = 0.471$ and $p = 0.768$, respectively) and mortality ($p = 0.495$ and $p = 0.268$, respectively). We did not find significant differences in inflammatory markers and secondary complications within the five groups.

Abbreviations: BIA, Bioimpedance Analysis; BMI, Body Mass Index; CAP, Community Acquired Pneumonia; ICU, Intensive Care Unit; LOS, Length of stay; MS, Metabolic Syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SP, sarcopenia; VAP, Ventilator Associated Pneumonia; VAT, Visceral Adipose Tissue; WC, Waist Circumference.

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Conclusions: In patients admitted with COVID-19, increased WC, visceral abdominal fat and SP are associated with higher need for ventilatory support. However, obesity, MS, SP and abdominal adiposity are not sensitive predictive factors for mortality.

1. Introduction

Obesity has reached epidemic levels and has been associated with a significant increase in morbidity and mortality in developed countries. As regards respiratory infections and past pandemics, obesity has shown an association with severe disease regarding the H1N1 influenza virus, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [1–3]. In the course of the ongoing pandemic, robust evidence has identified obesity as a common risk factor for negative outcomes in infections caused by SARS-CoV-2 (COVID-19) [4]. However, as regards mortality, the relationship with obesity in COVID-19 is still unclear, since some studies demonstrated a negative [5] or neutral impact [6,7], near to the so-called "obesity paradox", which is the inverse correlation between body mass index (BMI) and mortality, already described in infectious [8,9] and non-infectious diseases [10,11]. These conflicting results might be explained by the questionable use of BMI, since it does not distinguish between visceral and subcutaneous fat tissue. Actually, BMI is a poor discriminator of metabolically active visceral adipose tissue (VAT) and may not capture its complex action in response to viral infections, its implications in COVID-19 acute lung injury and critical illness due to both a mechanical and a metabolic action [12]. Sarcopenia (SP), defined as low muscle mass, has also been associated with a poor response to acute infections and to COVID-19 [13]. VAT can be easily evaluated through inexpensive anthropometric measurements, such as waist circumference (WC), or with more sophisticated methods, such as bioimpedance analysis (BIA), a practical non-invasive bedside tool to study body composition, including muscle mass. However, the available literature provides evidence mainly with BMI-measured obesity or metabolic syndrome (MS), and there are limited data on the role of VAT and SP in COVID-19 patients. Therefore, the aim of this study was to determine the impact of obesity, MS and VAT measured with different techniques (WC and BIA) and SP on clinical outcomes and mortality, including inflammatory markers, among patients admitted with COVID-19.

2. Methods

2.1. Setting, patients and data collection

We performed a prospective cohort study in a tertiary-care teaching hospital (Udine, Italy, 1000 beds) designated as a regional centre for COVID-19 patients and serving approximately 350,000 citizens. A cohort of all consecutive adults (≥18 years) with a diagnosis of COVID-19 admitted at the Infectious Disease Department including a regular ward and a subintensive care unit from 16 January 2021 to 15 February 2021 were eligible. Methods and findings are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [14].

Patients who were willing to participate were included and a database concerning their anthropometric, demographic, clinical, laboratory and radiological data was populated. Furthermore, BIA was performed at the bedside for a subgroup of patients by two trained nurses within 36 h of admission. Height, weight and WC were recorded and filled in for each patient's form into the SECA ® (model mBCA 525) device. Then, four adhesive and disposable electrodes were placed on the dorsal surface of the hand and right foot on dry and disinfected skin in supine patient with legs, hands and arms away from the body.

We excluded from the BIA analysis patients who were not able to collaborate or with a contraindication to the performance of BIA (pacemakers, arthroprotesis, and ECG monitoring) (Fig. 1).

2.2. Clinical definitions, classifications and outcomes

Obesity was defined as a BMI >30 kg/m^2 [15]. Increased WC was defined as >102 cm for men or >88 cm for women. MS was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III 2003 definition as the presence of three or more of the following risk factors: a) WC > 102 cm for men or > 88 cm for women; b) triglycerides ≥150 mg/dL; c) HDL cholesterol <40 mg/dL in men or < 50 mg/dL in women; d) hypertension ≥130/≥ 85 mmHg; and e) fasting glucose ≥110 mg/dL [16]. Body composition analysis was performed with a fixed frequency device, SECA® (model mBCA 525; Seca gmbh & Co, Hamburg, Germany), using a tetrapolar method. Tetrapolar hand to foot measurements were obtained in subjects who were supine for 15 min. This type of device enabled analysis of the whole body, and thereby the calculation of skeletal muscle

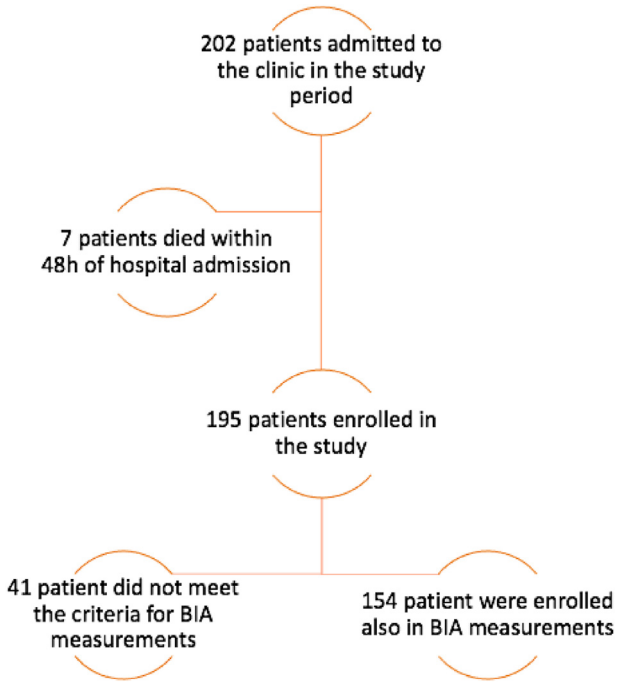

Fig. 1. Flowchart of patients admitted to the Infectious Disease Clinic between January and February 2021. BIA: bioimpedance analysis.

mass, taking segmental muscle mass into account. SP was defined as skeletal muscle mass (SMM) to BMI ratio (SMM/BMI) of 1.05 kg/kg/m^2 cut-off for men or 0.71 kg/kg/m^2 for women [17]. The study population was divided in five groups according to: 1) obesity, 2) WC, 3) MS, 4) fat distribution based on BIA and 5) SP. A confirmed case of COVID-19 was defined as a patient with a positive nucleic acid amplification test (NAAT) for SARS-CoV-2 in respiratory tract specimens. Clinical severity was classified according to the WHO COVID severity index [18]. ARDS was defined as the ratio of arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) as defined by the Berlin criteria [19]. Ventilatory outcomes were categorized according to the ordinal scale of the WHO Master Protocol for hospitalized patients including the most intensive support for each patient [1]: room air [2], oxygen support with nasal cannula or simple facial mask from an oxygen concentration of 24% up to 60% [3], high-flow oxygen devices (facial mask with oxygen concentration >60%, high flow nasal cannula and continuous positive airway pressure and non-invasive ventilation) and [4] invasive mechanical ventilation [20]. Patients were then followed up during their hospital stay and 30 days after their discharge. The primary outcome was to describe the impact of BMI, MS, WC, fat mass distribution based on BIA and SP in relation with ventilatory support, need for ICU admission and in-hospital 30-day mortality. Secondary outcomes included evaluation of immune and inflammatory markers, infectious (bacterial and fungal superinfections) and non infectious complications (cardiac, pulmonary and neurologic acute complications) within the four groups.

2.3. Laboratory methods

Identifying cases of COVID-19 was based on the detection of unique sequences of virus RNA by nucleic acid amplification test (NAAT), such as real-time PCR (RT-PCR), on respiratory samples. Genes were investigated as follows: E gene for screening and then RdRp and N genes of SARS-CoV-2 for confirmation. The viral RNA was extracted by using automated RNA extraction with the ELITe InGenius® SP200 System (ELITechGroup) and RT-qPCR was performed using a LightMix® Modular SARS and Wuhan CoV E-gene kit on a LightCycler® 480 II instrument (Roche). The specimens were considered positive if the cycle threshold (Ct) value for at least one of the three genes was $\leq$36. The RT-PCR was conducted as recommended by the World Health Organization for COVID-19 clinical management and outbreak control purposes.

Blood samples were analysed at admission, including flow cytometry analysis with antibodies for the following subpopulations: CD19+ B cells, CD3+ CD4+ T cells, CD3+ CD8+ T cells and CD56+ NK cells. MR-proADM plasma concentrations were measured in an automated Kryptor analyser, using TRACE technology (Kryptor; BRAHMS, Hennigsdorf, Germany). The cut-off for physiological concentration was 0.56 nmol/L. A microfluidic ultrasensitive ELISA using the Protein simple plex technology on ELLA instrument (R&D systems, Biotechne, USA) was used to assess the following cytokines and chemokines: Interleukin-1 beta (IL-1 beta, normal range <0.16 pg/mL), Interleukin-6 (IL-6, normal range <7 pg/mL), Interleukin-8 (IL-8, normal range 7–16 pg/mL), Tumor Necrosis Factor alpha (TNF-alpha, normal range 8–12 pg/mL), C-X-C Motif Chemokine Ligand 10 (CXCL10, normal range 37–222 pg/mL), Interferon gamma (IFNg, normal range <0.99 pg/mL), Interleukin-10 (IL-10, normal range 1.8–3.8 pg/mL), sIL-2R-alfa/sCD25 (normal range 440–1435 pg/mL). The tryptase (normal range <11.4 μg/L) was analysed by a diagnostic fluoroenzymeimmunoassay (ImmunoCap, Thermo Scientific). All the other laboratory biomarkers were evaluated using routine certified diagnostic methods.

2.4Ethical statement

This study was approved by the Ethics Committee of the Friuli Venezia Giulia Region (CEUR-2021-Os-78). All procedures were carried out in accordance with the ethical standards of the University of Udine, the ASUFC and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

2.5. Statistical analysis

The study population was divided in four groups according to obesity, WC, MS and SP. Absolute values, percentages, means and medians (standard deviations (SDs) or interquartile ranges (IQRs)) were calculated. Categorical variables were compared using the chi-squared test or Fisher's exact test, while continuous variables were compared using the Student t-test or Mann–Whitney U test, according to the Shapiro–Wilk test establishing whether data were normally or non-normally distributed. A univariable linear regression was performed to explore variables associated with the BIA parameters. Analyses were performed by STATA 17.

3. Results

3.1. Baseline characteristics of the four groups of patients

Over the study period, 202 patients were admitted to our clinic with a confirmed diagnosis of COVID-19 infection. Overall, 154 patients were eligible for BIA as 41 had a contraindication or were not able to collaborate (Fig. 1). Characteristics of the BIA parameters are described in Table 1.

The main general characteristics of the study population are shown in Table 2 and Supplementary Table 1. Overall, the median patient age was 71 years (IQR 61–80 years), 64.6% of patients were male and the mean BMI was 26.9 (24.2–31.3) kg/m^2. In all, 31.4% of patients were obese, 55.4% of patients were affected by MS, 60.6% of patients had an increased WC, mean VAT was 3.1 (1.9–4.3) L, mean FMI was 7.8 (5.8–10.7) and 68.9% of patients had SP according to our definition. Obese patients were younger (66 years, IQR 57–76 vs 73 years, IQR 63–82), had a lower CCI (3, IQR 2–4 vs 4, IQR 3–6) and a higher prevalence of MS (76.3% vs 48.1%). Patients with a higher WC were less frequently men (57.4% vs 83.6%); were more affected by hypertension (63.8% vs 44.3%), type 2 diabetes mellitus (38.3% vs 13.6%) and MS (80.8% vs 32.8%); and were less likely smokers (0% vs 9.3%). Patients with hypertension had an increased VAT and FMI ($p = 0.016$ and $p = 0.031$, respectively). An increased FMI was also associated with smoking ($p = 0.032$), alcohol use disorder ($p = 0.025$), MS ($p < 0.001$) and hypertension. Patients with a more severe presentation according to the WHO grading severity scale had an increased VAT ($p = 0.018$). Sarcopenic patients

Table 1
Characteristics of the BIA parameters (total 154 patients).

BIA parameter	Median (IQR)
Relative fat mass value (kg/m^2)	29.2 (22.0–35.0)
Absolute fat mass value (kg)	23.0 (17.0–31.7)
Fat free mass (kg)	58.7 (48.4–68.0)
Skeletal muscle mass (kg)	27.4 (20.8–32.2)
Total Body Water (L)	43.4 (36.5–50.2)
Extracellular water (L)	19.3 (16.8–21.8)
FFMI (kg/m^2)	19.7 (17.5–21.9)
FMI (kg/m^2)	7.8 (5.8–10.7)
Phase Angle (°)	5.5 (4.6–6.3)
Visceral adipose tissue (L)	3.1 (1.9–4.3)

BIA bioimpedance analysis, FFMI, free fat mass index; FMI fat mass index, IQR interquartile range.

Table 2
Clinical and radiological characteristics and treatment of the 195 patients admitted to our clinic during the study period, univariable linear regression of BMI, waist circumference, metabolic syndrome and sarcopenia and linear regression of VAT and FMI.

	Patients (n = 195)	BMI <30 (n = 129/188, 68.6%)	BMI >30 (n = 59/188, 31.4%)	p	Non-MS (n = 87/195, 44.6%)	MS (n = 108/195, 55.4%)	P	Normal WC[a] (n = 61/155, 39.4%)	Increased WC[b] (n = 94/155, 60.6%)	p	VAT[c]	p	FMI[c]	p	SP[d] (n = 47)	Non-SP[d] (n = 104)	p
Age, years, median (IQR)	71 (61–80)	73 (63–82)	66 (57–76)	*0.007*	68 (58–78)	71.5 (63.5–81)	*0.106*	69 (57–78)	70 (59–80)	*0.610*	−0.01	*0.686*	0.01	*0.737*	78 (65–84)	67.5 (57–75)	<0.001
Sex, male, n (%)	126 (64.6)	81 (62.8)	41 (69.5)	*0.372*	62 (71.3)	64 (59.3)	*0.081*	51 (83.6)	54 (57.4)	*0.001*	−1.63	*<0.001*	3.26	*<0.001*	20 (42.5)	30 (28.8)	0.097
CCI, median (IQR)	4 (2–5)	4 (3–6)	3 (2–4)	*0.041*	3 (2–4)	4 (3–6)	0.020	3 (2–4)	3 (2–5)	*0.451*	0.05	*0.444*	−0.04	*0.755*	4 (3–6)	3 (1–4)	<0.001
Diabetes, n (%)	50 (25.6)	29 (22.5)	19 (32.2)	*0.174*	6 (7.1)	44 (40.7)	*<0.001*	8 (13.6)	36 (38.3)	*0.001*	0.43	*0.226*	1.10	*0.128*	20/46 (43.5)	24/103 (23.3)	0.013
MS, n/N (%)	108 (55.4)	62 (48.1)	45 (76.3)	*<0.001*	–	–	–	20 (32.8)	76 (80.8)	*<0.001*	1.18	*<0.001*	3.01	*<0.001*	37 (78.7)	57 (54.8)	0.005
BMI, median (IQR)	26.9 (24.2–31.3)	–	–	-	25.9 (23.1–28.1)	28.8 (25.1–32.7)	*<0.001*	26 (19–30)	30.7 (26.7–33.9)	*<0.001*	0.26	*<0.001*	0.59	*<0.001*	28.1 (25.7–32.3)	26.7 (24.4–31.5)	0.181
WC, median (IQR)	1.01 (0.92–1.1)	0.97 (0.9–1.02)	1.13 (1.07–1.22)	*<0.001*	0.98 (0.91–1.02)	1.06 (0.95–1.14)	*<0.001*	–	–	-	9.66	*<0.001*	11.15	*<0.001*	*1.01 (0.95–1.09)*	*1.01 (0.91–1.10)*	*0.957*
Sarcopenia	104/151 (68.9)	71/101 (70.3)	33/50 (66.0)	*0.591*	47/57 (82.5)	57/94 (60.6)	*0.005*	43/58 (74.1)	61/93 (65.6)	*0.270*	−0.35	*0.317*	−3.49	*<0.001*	-	-	-
WHO severity[e]				*0.534*			*0.082*			*0.150*	0.38	*0.018*	0.32	*0.325*			0.054

BMI, Body mass Index; CCI, Charlson Comorbidity Index; COPD, Chronic obstructive pulmonary disease; LMWH, low molecular weight heparin; FMI, fat mass index; IQR, interquartile range; MS, Metabolic syndrome; P/F, arterial oxygen partial pressure to fractional inspired oxygen ratio; SMM, skeletal muscle mass; SP, sarcopenia; VAT, visceral abdominal tissue; WC, waist circumference; WHO, world health organization.

[a] Normal waist circumference: < 102 cm for men, < 88 cm for women.

[b] Increased waist circumference: > 102 cm for men, > 88 cm for women.

[c] Analysis available on 154 patients, β coefficient.

[d] SP defined as SMM/BMI <1.05 kg/kg/m^2 for men and <0.71 kg/kg/m^2 for women.

[e] Disease severity scale [18].

were older (78 years, 65–84 vs 67.5 years, 57–75); p < 0.001), were more affected by MS (p = 0.005) and had a lower FMI (p < 0.001). We did not find differences with regard to presentation, radiological severity and treatment, except for corticosteroids which were more frequently prescribed in all groups of increased adiposity (Table 2 and Supplementary Table 1).

3.2. Ventilatory support, outcomes and mortality

Overall, most patients needed oxygen therapy (88.2%) and 31 (15.9%) patients required invasive mechanical ventilation (Table 3 and Supplementary Table 2). The median length of hospital stay was 10 [5–20] days, and 31 (16%) patients were admitted to the ICU, with a median ICU stay of 27.5 [19–46] days. The mortality rate was 19.5% (Table 3). In the univariate analysis, patients with a higher WC had a lower P/F ratio at admission (290.5, IQR 266.7–333.3, p ≤ 0.001 vs 338.1, IQR 304.8–376.2).

Ventilatory support was higher in the increased WC group (p = 0.013), at increasing VAT (p = 0.037 for nasal canula and face mask, p = 0.027 for high-flow oxygen device and non-invasive ventilation and p = 0.009 for invasive mechanical ventilation) and FMI (p = 0.004 for nasal canula and face mask and p = 0.036 for high-flow oxygen device and non-invasive ventilation) and in patients with SP (p = 0.051) (Table 3). Higher WC, VAT and FMI, as well as the presence of SP were not associated with mortality. Of note, obesity and MS were associated with neither increased ventilation (p = 0.142 and p = 0.198, respectively) nor with mortality (19.4% of non-obese patients vs 15.2% of obese patients, p = 0.495; 23% of patients without MS vs 16.75 of patients with MS, p = 0.268). Higher BMI, WC, VAT and FMI or the presence of MS and SP were associated with neither a higher rate of ICU admission nor longer hospital or ICU stays (Table 3). Clinical outcomes according to BIA parameters are available in Supplementary Table 3.

3.3. Immune and inflammatory response

Higher circulating monocytes were found in patients with BMI >30 (p = 0.002) and with increasing FMI (p = 0.027), while higher CD4+ lymphocytes count was found in increasing FMI (p = 0.037). Lower NK lymphocyte counts and HDLAR were observed in SP (p = 0.046 and p = 0.032, respectively). We were able to discern, in 157 patients, the levels of several cytokines and chemokines. We found no significant difference in the population, with the exception of CXCL10, higher in patients with MS (p = 0.006), IL-10, lower in patients with higher VAT (p = 0.021) and FMI (p = 0.024) and higher levels of pro-adrenomedullin in patients with SP (1.24 nMol/L (0.87–1.68) vs 0.96 (0.8–1.2), p = 0.004). No significant difference in other cytokines or inflammatory parameters was found between the groups (Table 4 and Supplementary Table 4).

3.4. Infectious and non-infectious complications

Secondary infectious and non-infectious acute complications occurred in 18 (9.2%) and 26 (13.3%) patients, respectively. The rate of acute complications was not statistically different between the groups, as shown in Supplementary Table 3.

4. Discussion

In our prospective observational study on patients admitted with COVID-19, we described clinical outcomes and mortality according to obesity, MS, adiposity distribution and SP measured through different methods, including BIA. We found that the amount of VAT and pathological WC, as well as SP, are more sensitive parameters to predict the need for high ventilatory support

Table 3
Ventilatory support, outcome and complications of the 195 patients admitted to our clinic during the study period, univariable linear regression of BMI, waist circumference and metabolic syndrome and linear regression of VAT and FMI.

Outcome	Patients (n = 195)	BMI <30 n = 129/188, 68.6%)	BMI >30 (n = 59/188, 31.4%)	*P*	Non MS (n = 87/195, 44.6%)	MS (n = 108/195, 55.4%)	*p*	Normal WC[a] (n = 61/155, 39.4%)	Increased WC[b] (n = 94/155, 60.6%)	*p*	VAT[c]	*p*	FMI[c]	*p*	SP[g] (n = 47)	Non-SP[g] (n = 104)	*p*
Oxygen support[d]				*0.142*			*0.198*			*0.013*		*0.009*		*0.004*			*0.051*
ARDS, n/N	3 (1.8)	0/107 (0)	3/54 (5.6)	*0.036*	0/71 (0)	3/94 (3.2)	*0.260*	0/50 (0)	2/85 (2.3)	*0.274*	−2.68	*0.059*	−2.80	*0.326*	0 (0)	2 (2.2)	1.000
ICU admission, n	31 (16.0)	20 (15.5)	10 (16.9)	*0.802*	14 (16.1)	17 (15.7)	*0.947*	8 (13.1)	15 (16.0)	*0.627*	0.64	*0.153*	−0.58	*0.519*	7 (14.9)	16 (15.4)	0.938
Total LOS, median, days	10 (5–20)	10 (6–23.5)	11 (5–18)	*0.471*	9 (5–23)	10 (6–18)	*0.768*	8.5 (5–20)	11 (6–18)	*0.345*	−0.01	*0.650*	−0.03	*0.159*	10 (6–14)	9.5 (5–19.5)	0.992
ICU LOS, median, days	27.5 (19–46)	29 (20–46)	22.5 (18–55)	*0.730*	27.5 (20–41)	27.5 (18.5–50.5)	*0.851*	26 (24–43)	24 (17–46)	*0.323*	−0.01	*0.693*	−0.02	*0.407*	35 (18–43)	25 (19.5–39.5)	0.658
Mortality, n[f]	38 (19.5)	25 (19.4)	9 (15.2)	*0.495*	20 (23.0)	18 (16.7)	*0.268*	6 (9.8)	15 (16.0)	*0.277*	0.30	*0.533*	−0.05	*0.957*	9 (19.1)	12 (11.5)	0.211

ARDS, acute respiratory distress syndrome, BMI, Body mass Index; FMI, fat mass index; HFOD, High-flow oxygen device; ICU intensive care unit; IMV, Invasive mechanical ventilation; IQR, interquartile range; LOS length of stay; LTCF long term care facility; NIV, non-invasive ventilation; P/F, arterial oxygen partial pressure to fractional inspired oxygen ratio; SMM, skeletal muscle mass; SP, sarcopenia; VAT, visceral abdominal tissue; WC, waist circumference.
All values are expressed as median (IQR) or number (percentage).
[a] Normal waist circumference: < 102 cm for men, < 88 cm for women.
[b] Increased waist circumference: > 102 cm for men, > 88 cm for women.
[c] Analysis available on 154 patients, β coefficient.
[d] The most intensive during the hospital stay.
[f] All-cause in-hospital and 30-day mortality.
[g] SP defined as SMM/BMI <1.05 kg/kg/m^2 for men and <0.71 kg/kg/m^2 for women.

than BMI and MS. In contrast, we did not find a higher rate of mortality in patients affected by obesity, MS, SP or increased VAT, even when fat tissue was measured with different techniques.

Risk factors for poor prognosis in COVID-19 patients have been investigated since the beginning of the pandemic. Obesity and MS are among the most common comorbidities among COVID-19 patients, with the prevalence of obesity ranging from 21.6% in European studies to 41.7% in US studies and MS accounting for 47.1%–65% in large studies of hospitalized patients [21–24]. Obesity has been found to be a relevant predictor for the need of invasive mechanical ventilation [25], longer hospitalization, increased rate of ICU admission and stay [26]. MS is related to more severe forms of COVID-19 with a proportional increase with increasing MS components and up to a 4-fold higher rate in some series [23,24]. Interestingly, the real impact of MS in countries whose prevalence is high is still unclear, as lower rates of COVID-19 cases in low MS prevalence countries may be due to less efficient systems of reporting [27]. A common limitation of these studies is the definition of obesity with BMI, which is known to be a poor discriminator of visceral adiposity [28]. In contrast, our study indicates that obesity and MS are not associated with higher intensive oxygen support, but this association is significant in patients with excessive abdominal adiposity.

In our study, WC showed a strong association with intensive ventilatory support. In line with our findings, Malavazos et al. and Van Zelst and colleagues found that central obesity measured through WC was the best predictor for the radiological severity of disease and negative outcome, respectively [29,30]. Advocated as a vital sign in clinical practice, the measurement of WC is a simple, inexpensive, bedside and easily standardizable method that is considered important for risk stratification [28].

Previous retrospective studies have identified high VAT on CT scan as predictors of need for hospitalization [31], ICU admission [32] and mechanical ventilation [33]. To the best of our knowledge, this is the first study to suggest the negative impact of increased VAT and FMI measured by BIA on the outcome of COVID-19. However, there are very limited data on BIA, which is a novel non-invasive technique able to describe in detail the amount of fat mass, lean mass (i.e., muscle and bone) and their distributions without the use of X-rays. Moonen and colleagues, including ICU and regular ward COVID-19 patients, found no association between body composition analysed with BIA and disease severity [34]. However, along with the findings of Cornejo-Pareja et al., a lower phase angle was associated with COVID-19 severity [35]. In contrast with these latter studies, we did not find any association with phase angle and disease prognosis, while we did find a longer LOS in increasing phase angle and a risk of more invasive ventilation for every additional VAT or FMI unit. This association suggests that VAT may play a dual role in the acute lung injury and in the critical illness due to both its mechanical and metabolic actions. VAT is a metabolically active organ with known implications for the risk of cardiovascular and metabolic diseases [36]. Augmented VAT causes increased chest pressure, decreasing expiratory reserve volume and the compliance of ventilation [12]. Moreover, adipocytes express on their surface the angiotensin-converting enzyme 2 (ACE2), the receptor which SARS-CoV-2 uses to enter cells, and as such, they are believed to be a viral reservoir [12]. In our cohort, excess adiposity, regardless of the method used to measure it, did not show any association with mortality. The impact of obesity on mortality in COVID-19 is still argued. The description of clinical phenotypes of COVID-19 and early reports have described obesity as a risk factor for mortality [21,37]. On the other hand, other studies, while confirming a higher rate of invasive ventilation and ICU admission among obese patients, found a similar rate of death in obese and lean patients [6,7,26]. The lack of negative influence of obesity on

Table 4
Laboratory parameters of the 195 patients admitted to our clinic during the study period, univariable linear regression of BMI, waist circumference and metabolic syndrome and regression of VAT and FMI.

	Patients (n = 195)	BMI <30 (n = 129/188, 68.6%)	BMI >30 (n = 59/188, 31.4%)	*p*	Non MS (n = 87/195, 44.6%)	MS (n = 108/195, 55.4%)	*p*	Normal WC[b] (n = 61/155, 39.4%)	High WC[c] (n = 94/155, 60.6%)	*p*	VAT[d]	*p*	FMI[c]	*p*	SP[e] (n = 47)	Non-SP[e] (n = 104)	*p*
Pro-ADM, nMol/L	1.0 (0.8–1.4)	1.0 (0.8–1.5)	1 (0.8–1.3)	*0.533*	1.0 (0.8–1.4)	1.1 (0.9–1.5)	*0.123*	0.9 (0.8–1.3)	1.0 (0.9–1.4)	*0.233*	−0.20	*0.259*	0.24	*0.505*	1.24 (0.87–1.68)	0.96 (0.8–1.2)	*0.004*
IL-1 beta[a], pg/mL	0 (0–0.8)	0 (0–0.1)	0 (0–0.01)	*0.110*	0 (0–0.11)	0 (0–0.02)	*0.108*	0 (0–0.1)	0 (0–0.02)	*0.128*	−2.12	*0.180*	−3.74	*0.216*	0 (0–0.02)	0 (0–0.05)	*0.862*
CXCL10[a], pg/mL	1193 (739–1776)	1280 (581–1794)	1176 (819–1757)	*0.767*	1027 (489.0–1619.5)	1313 (958–1966)	*0.006*	1128 (476–1672)	1242.5 (939–1767)	*0.115*	0.00	*0.637*	0.00	*0.769*	1213.5 (918–1920.8)	1255 (739–1733)	*0.347*
IL-10[a], pg/mL	15.1 (9.0–23.7)	15.3 (8.6–25.3)	14.1 (9.0–19.7)	*0.450*	15.2 (7.3–23.3)	15.0 (9.6–23.7)	*0.578*	13.4 (7.1–19.8)	14.6 (9.6–22.4)	*0.196*	−0.01	*0.021*	−0.03	*0.024*	13.1 (7.2–19.2)	15.3 (9.5–23)	*0.175*
Monocytes/μL	400 (270–685)	370 (210–525)	532 (333–738)	*0.002*	416 (270–560)	400 (274.5–720)	*0.435*	339 (210–522)	430 (300–720)	*0.021*	0.00	*0.136*	0.01	*0.027*	380 (300–700)	400 (261–680)	*0.374*

BMI, Body mass Index; CHOL, cholesterol; CRP, C-Reactive Protein; CXCL10, C-X-C Motif Chemokine Ligand 10; FMI, fat mass index; HbA1c, glycated hemoglobin; HDL high-density lipoprotein; IL, Interleukin; IFN- γ, interferon-gamma; IQR, interquartile range; LDH, Lactate dehydrogenase; LDL, low-density lipoprotein; lympho, lymphocytes PCT, procalcitonin; PLT platelets; Pro-ADM, pro-adrenomedullin; SMM, Skeletal muscle mass; SP, sarcopenia; TCG, triglycerides; TNF-alfa, tumor necrosis factor-alfa; VAT, visceral abdominal tissue; WBC White blood cells.

[a] Available on 157 patients.
[b] Normal waist circumference: < 102 cm for men, < 88 cm for women.
[c] Increased waist circumference: > 102 cm for men, > 88 cm for women.
[d] Analysis available on 154 patients, β coefficient.
[e] SP defined as SMM/BMI <1.05 kg/kg/m^2 for men and <0.71 kg/kg/m^2 for women.

mortality or even the protective influence, known as the obesity paradox, has been already described in community-acquired, ventilator-associated pneumonia and ARDS with variable follow-up [8,9,38]. Consistent with these findings, we did not find a difference in mortality between obese patients and their lean counterparts or in patients with or without MS. However, in our cohort, excess adiposity, regardless of the technique used to measure it, was not a protective factor and was not even associated with an increase in mortality. To the best of our knowledge, this is the first study showing an "abdominal fat paradox", since no association between high VAT measured with different methods and mortality was found in COVID-19 patients. This paradox may have several explanations. First, there may be the influence of confounders and performance bias to give earlier and more aggressive treatment to obese patients [39]. In our study patients with excess adiposity were treated more frequently with corticosteroids and had lower a P/F ratio. Second, the low-grade inflammation environment of obese patients, which may become resilient if faced with an additional inflammatory insult. Third, the higher resistance of obese patients to the catabolic state of critical illness and, fourth, the immunomodulatory action of adipose tissue through hormones and cytokines, such as leptin and IL-10 with a possible anti-inflammatory role [39,40].

As regards SP, our results confirmed the previous findings of a negative impact of low muscle mass and the outcome of COVID-19 [13,41]. In addition to the obvious role of allowing respiratory contractions, likewise VAT, skeletal muscle is being considered as an endocrine organ with immunomodulatory and anti-inflammatory functions [42]. As such, we found higher pro-adrenomedullin levels in patients with SP, as described in severe forms of COVID-19 [43], and lower NK lymphocytes count and HLADR, as possible markers of immune exhaustion.

In our study, we found lower levels of IL-10 with increasing VAT and FMI and higher CXCL-10 in MS, as described by Blot et al. [44]. Other cytokines levels were not different between the remaining groups, which is probably due to the single determination of cytokines at admission, before the complete activation of the immune system. Moreover, cytokines may have both pro-inflammatory and anti-inflammatory roles, with a still unknown kinetic. In our cohort, higher CD4+ lymphocytes levels in patients with a higher FMI and higher monocytes in obese and higher FMI patients may be due to both the response to viral insult and the higher circulation of monocytes in obese patients due to their diapedesis stimulated by adipocytes, which will eventually become resident macrophages in the adipose tissue [45]. The study of secondary outcomes did not result in significant differences, which is probably due to the small number of events we recorded during the study period.

This study has several limitations. First, as a single centre study, the degree of obesity and adipose tissue in our patients may differ from others, and the results might be not generalizable. Second, the ethnicity of our cohort was homogeneous, and it may not reflect the disparities observed in other countries [46]. Third, due to inherent contraindications for the execution of BIA, we were not able to perform it on every patient. Fourth, our study was performed only on inpatients, without a comparison to an outpatient cohort. Fifth, our definition of SP did not include a measurement of muscle strength. Sixth, in our cohort the prevalence of obesity is relatively low (31.4%). Lastly, levels of blood triglycerides and fasting glucose may have been influenced by the stress of acute illness.

In this prospective study on the impact of obesity, MS and body composition on the clinical outcomes and mortality of patients with COVID-19, we found an abdominal adipose tissue paradox since WC and VAT were a risk factors for more intensive oxygen support, but not for mortality. We confirmed the association between SP and negative outcomes in COVID-19, but not mortality.

We found that the amount of visceral adiposity was a more sensitive parameter to predict the negative outcome of the disease than BMI. We advocate for the use of WC measurement as a predictive tool for the correct allocation of COVID-19 patients in clinical practice, as it is a simple, economical bedside tool. Further studies are needed to investigate the role of BIA measurements in critical illness and severe forms of COVID-19.

Authors contributions

Conceptualization; M. Peghin, E. Graziano; Data curation E. Graziano, C. De Carlo, L. Bulfone, V. Casarsa; Statistical analysis M. De Martino, M. Isola; Investigation M. Peghin, E. Graziano; Methodology M. Peghin, E. Graziano; Writing and Original Draft: E. Graziano, M. Peghin; Writing, Review & Editing: E. Graziano, M. Peghin; Supervision and critical review: M. Peghin, M. Isola, A. Da Porto, E. Graziano, A. Cifù; , M. Fabris, B. Grassi, C. Tascini, L. A. Sechi.

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Conflict of Interest

M.P. reports receiving grants and personal fees from Pfizer, MSD, Menarini and Dia Sorin outside the submitted work. C.T. has received grants in the last two years from Correvio, Biotest, Biomerieux, Gilead, Angelini, MSD, Pfizer, Thermofisher, Zambon, Shionogi, Avir Pharma and Hikma outside the submitted work. The other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.07.003.

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