RESEARCH

Low muscle mass and high visceral fat mass predict mortality in patients hospitalized with moderate-to-severe COVID-19: a prospective study

Fabyan Esberard de Lima Beltrão[1,2,3], **Daniele Carvalhal de Almeida Beltrão**[3,4], **Giulia Carvalhal**[5], **Fabyo Napoleão de Lima Beltrão**[6], **Igor Motta de Aquino**[7], **Thaíse da Silva Brito**[8], **Barbara Costa Paulino**[2], **Elisa Aires**[9], **Diana Viegas**[10], **Fabio Hecht**[11], **Bruno Halpern**[12], **Liana Clebia De Morais Pordeus**[4], **Maria da Conceição Rodrigues Gonçalves**[2] and **Helton Estrela Ramos**[9,13,14]

[1]Lauro Wanderley University Hospital, Federal University of Paraíba, João Pessoa, Paraíba, Brazil
[2]Postgraduate Program in Nutritional Sciences, Department of Nutrition, Center for Health Sciences, Federal University of Paraíba, João Pessoa, Paraíba, Brazil
[3]University Centre of João Pessoa (UNIPE), João Pessoa, Paraíba, Brazil
[4]Postgraduate Program in Cognitive Neuroscience and Behavior, Center for Health Sciences, Federal University of Paraíba, João Pessoa, Paraíba, Brazil
[5]Center for Biological and Health Sciences, Federal University of Campina Grande, Campina Grande, Paraíba, Brazil
[6]Department of Medicine, Faculty of Medical Sciences, João Pessoa, Brazil
[7]Metropolitan Hospital Dom José Maria Pires, Santa Rita, Paraíba, Brazil
[8]New Hope Medical School – FAMENE, João Pessoa, Paraíba, Brazil
[9]Postgraduate Program in Interactive Processes of Organs and Systems, Health & Science Institute, Federal University of Bahia, Salvador, Bahia, Brazil
[10]Internal Medicine Department, rede UniFTC, Salvador, Bahia, Brazil
[11]The Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[12]Weight Control Centre, Hospital 9 de Julho, São Paulo, São Paulo, Brazil
[13]Department of Biorregulation, Health Sciences Institute, Federal University of Bahia, Bahia, Brazil
[14]Postgraduate Program in Medicine and Health, Medical School of Medicine, Federal University of Bahia, Salvador, Bahia, Brazil

Correspondence should be addressed to H E Ramos: ramoshelton@gmail.com

Abstract

Introduction: The severity of coronavirus disease 2019 (COVID-19) has been positively correlated with several comorbidities. The primary outcome of the study was to assess the relationship between the mortality and severity of COVID-19 and obesity classes according to BMI, visceral adipose tissue (VAT) area, s.c. adipose tissue area, muscle area (MA), and leptin levels.

Methods: In this prospective cohort study, 200 patients hospitalized with moderate-to-severe COVID-19 underwent an unenhanced CT of the thorax and laboratory tests, and leptin levels between June and August 2020 were obtained.

Results: Our study included 200 patients (male 52%; mean age: 62 (49–74) years; obesity (BMI > 30): 51.5%)). Fifty-eight patients (23.5%) were admitted to the intensive care unit and 29 (14.5%) died. In multivariate logistic regression (corrected for leptin, sex, age, and serum biomarkers) and receiver operating characteristic curve analyses, high VAT > 150 cm^2 (odds ratio (OR): 6.15; $P < 0.002$), MA < 92 cm^2 (OR: 7.94; $P < 0.005$), and VAT/MA ratio > 2 (OR: 13.9; $P < 0.0001$) were independent risk factors for mortality. Indeed, the Kaplan–Meier curves showed that patients with MA < 92 cm^2 and without obesity (BMI < 30) had a lower survival rate (hazard ratio between 3.89 and 9.66; $P < 0.0006$) than the other groups. Leptin levels were not related to mortality and severity.

Key words
- visceral adipose tissue
- obesity
- COVID-19
- SARS-CoV-2

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Conclusion: This prospective study reports data on the largest number of hospitalized severe COVID-19 patients and pinpoints VAT area and MA calculated by CT as predictors of COVID-19 mortality.

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Introduction

A multisystem infectious disease is caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). To enter the host cell, SARS-CoV-2 binds to the cellular receptor of the angiotensin-converting enzyme 2 (ACE2). ACE2 expression in the adipose tissue is greater than that in lung tissue, which means that adipose tissue may be vulnerable to coronavirus disease 2019 (COVID-19) infection (1, 2, 3).

Obesity seems to predispose patients with SARS-CoV-2 infection to increased severity of this disease, including hospitalization, intensive care unit (ICU) admission, orotracheal intubations, and death (4, 5). BMI is commonly used to assess obesity, but fat distribution (visceral and s.c.) and body composition (the percentage of fat and fat-free mass) are risk factors considered more accurate than BMI to assess cardiometabolic risk (6, 7); indeed, there is evidence that differences in both body composition and fat distribution lead to different COVID-19 outcomes (8).

As an example, low lean mass and sarcopenia, although markers of frailty and aging, have also been independently associated with COVID-19 severity (9); importantly, obesity and sarcopenia can coexist in the same individual, worsening the overall prognosis (10). In large medical centers around the world, the prevalence of patients with obesity admitted to the ICU was over 40% of the occupied beds (11, 12) and greater than 60% in sarcopenic patients (13, 14).

Regarding visceral fat, a small research study used low-dose chest CT in hospitalized patients and observed that every 10 cm^2 increase in visceral fat was associated with a 1.37-fold higher likelihood of ICU (14, 15).

In an Italian study, VAT was independently (multivariate logistic regression) associated with the need for intensive care in patients with COVID-19 (odds ratio (OR): 2.47; 95% CI: 1.01–6.01; $P=0.046$) (8). Visceral fat is a proxy of ectopic fat deposition and is associated with insulin resistance, nonalcoholic steatohepatitis, and overall systemic inflammation, factors that could have a causal role in the overall worse prognosis seen in epidemiological studies (16, 17).

Several techniques have been developed to assess muscle mass and different types of fat, among which dual-energy X-ray absorptiometry, CT, and MRI provide a more accurate estimation of assessing body composition, as well as the area and density of these body tissues (18).

Leptin is a peptide produced mainly in adipose tissue that has structural similarities to members of the family of long-chain helical cytokines. Leptin acts by decreasing appetite and stimulating thermogenesis, in addition to participating in several physiological processes, including inflammation, angiogenesis, hematopoiesis, osteogenesis, reproduction, and immune function (19, 20). Nonetheless, in obesity, leptin is almost universally high, and obesity is considered a state of leptin resistance. Zhang and coworkers studied the pathogenesis of 2009 influenza A (H1N1) infection in a high-fat diet-induced obesity model in mice and found that hyperleptinemia was associated with increased mortality, viral shedding, and severe lung injury caused by H1N1 (21).

Our primary objective was to analyze the association between body composition (derived from thoracic CT), leptin levels, mortality, immunological changes, and outcomes in moderate-to-severe COVID-19 hospitalized patients.

Materials and methods

Subjects and data collection

Our study was an offshoot of another study designed to assess thyroid dysfunction in patients with inhospital COVID-19 (22). An observational, longitudinal, and prospective cohort study was conducted between June and August 2020, and we enrolled 200 consecutive patients with confirmed COVID-19 admitted to the Hospital Metropolitano Dom José Maria Pires, a tertiary referral hospital in João Pessoa, Paraíba, Brazil (Supplementary Fig. 1, see section on supplementary materials given at the end of this article). A written consent form was obtained from the participants or a legal representative. The study was approved by the Human Research Ethics Committee of the Lauro Wanderley University Hospital (CAAE: 31562720.9.0000.5183).

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Inclusion and exclusion criteria

All patients tested positive for SARS-CoV-2 using the real-time quantitative reverse-transcriptase-PCR (rRT-qPCR) with samples from the respiratory tract and, in cases of negative rRT-qPCR, using clinical, radiological, and serological (IgG positive for SARS-CoV-2) criteria. The rRT-qPCR kit used was the Biomol OneStep COVID-19 kit (IBMP, Paraná, Brazil). Patients with a history of thyroid disease, who used iodinated contrast in the last 6 months or drugs that interfere with thyroid metabolism, and diagnosis of pregnancy were excluded.

Procedures

The detailed clinical information of each patient was obtained by physicians using a standard questionnaire. Upon admission of patients to the hospital, the Quick Sepsis-Related Organ Failure Assessment (q-SOFA) scale and the National Early Warning Score 2 (NEWS2) scale were used.

All cases were from moderate-to-severe patients who were divided into two clinical classifications: noncritical and critical. For noncritical cases, patients who met any of the following criteria were considered: respiratory rate > 30 cycles/min, oxygen saturation <93% at rest, partial arterial oxygen pressure (PaO_2)/oxygen concentration (FiO_2) < 300 mmHg, and extension of lung injury by COVID-19 estimated >50%. Critical outcomes were defined as ICU care or death.

Serum biochemistry

All the 200 patients underwent assessment of leptin, interleukin-6 (IL6), D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase, creatinine, high-sensitivity C-reactive protein (hs-CRP), and lactate dehydrogenase (LDH). Leptin was measured with an ELISA (DiaSorin, Inc., Stillwater, Minnesota, USA). The method used in the other exams was automated chemiluminescence (MAGLUMI-2000-PLUS; Shenzhen New Industries Biomedical Engineering Co., Shenzhen, China). Measurements were performed according to the manufacturer's protocol.

The number of neutrophils and lymphocytes, the neutrophil–lymphocyte ratio (NLR), and hemoglobin levels of all patients were recorded.

Image analysis

The patients underwent CT scans of the thorax to diagnose suspected SARS-CoV-2 pneumonia. We considered the following thoracic CT patterns: ground-glass opacity, mosaic attenuation, and consolidation. In all cases, a semiquantitative CT severity score was proposed by Pan and coworkers (23). All chest CT scans were performed using a 64-detector CT scanner (Revolution EVO, General Electric) with the following parameters: 120 kV, 350 mAs, rotation time 0.4 s, pitch 1.5, and slice thickness 2–5 mm. The technical parameters of CT acquisition were adjusted according to the clinical problem under investigation and patient body size.

The assessment of the visceral adipose tissue (VAT) area, s.c. adipose tissue (SAT) area, and muscle area (MA) with thorax CT was performed by an experienced radiologist (more than 10 years) using AW VolumeShare 7 (General Electric Healthcare) and 3DSlicer® software (The Slicer Community, Harvard, MA, USA) and a previously described method (15). To quantify visceral and s.c. abdominal fat and MA (abdominal muscles excluding the psoas muscle), the first slice in which the lung bases were no longer visible at the thoracoabdominal level (between T12 and L2) was selected. On each image, a region of interest (ROI) was manually drawn over the abdominal wall to delineate the interface between the abdominal wall and the abdominal fat. No extreme precision is needed in this phase because the difference in density/intensity between the abdominal wall and the abdominal fat is high on CT. The region growing (segmentation) algorithm was selected, thus allowing the segmentation ROIs to be drawn with a semiautomated method.

The tissue cross-sectional areas were analyzed using tissue-specific Hounsfield unit (HU) attenuation ranges, which were defined according to the values established in the literature: (i) VAT to SAT between –50 and –250 HU and (ii) skeletal muscle between –29 and 150 HU. Regarding the muscular component, the erector muscles of the spine, latissimus dorsi, external and internal oblique, rectus abdominis, and external and internal intercostal muscles were evaluated (15, 24). Data for the selected tissue, including surface area, were expressed in square centimeters (cm^2), and the relative distribution of abdominal adipose tissue was assessed by using the VAT/SAT ratio (Supplementary Fig. 1).

Statistical analysis

To calculate the sample size, the GPower 3.1.9.7 software (Heinrich-Heine-Universität, Düsseldorf, Germany) was used. As significance criteria, alpha = 0.05, power = 0.95, and F2 = 0.10 were assumed, and the proposed minimum sample size was 158 patients. Data were expressed as

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median ± interquartile range. In the quantitative analysis, nonparametric tests were used: Mann–Whitney test for only two variables and Kruskal–Wallis test followed by Dunn's multiple comparisons test for more than two variables. In the nonparametric qualitative analyses, the Fisher's test was employed. Spearman's test was applied to assess the linear correlation coefficient between the analyzed variables, and univariate and multivariate logistic regression analyses were used to assess the relative risk of mortality.

To assess the prognostic impact of the variables on inhospital mortality, Kaplan–Meier survival analysis and receiver operating characteristic (ROC) curve analysis were used with the estimation of the area under the curve, sensitivity, and specificity of the variables in relation to mortality. A significance level of $P < 0.05$ was accepted as statistically significant. GraphPad Prism version 7.00 (2016) was used to perform the statistical tests.

Results

A total of 274 adult patients admitted with COVID-19 in a reference hospital were considered eligible for the study, and after evaluating the inclusion and exclusion criteria, 200 consecutive patients remained in the study (Fig. 1). During follow-up, the average length of stay of patients in hospital was 8.5 days, 44 (22%) patients were admitted to the ICU, and 29 (14.5%) patients died. The median age of patients was 62 (50 –74) years and 113 patients (56.5%) were male (Table 1).

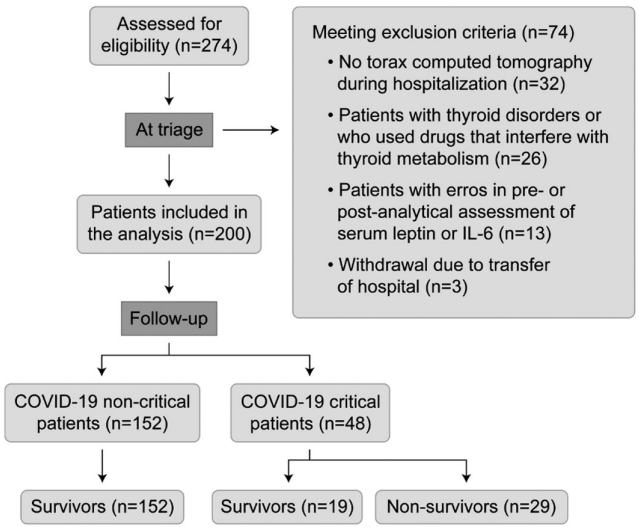

Figure 1
Flowchart of the study. COVID-19, coronavirus disease-19; IL6, interleukin-6.

Statistical analysis was performed to investigate the risk factors associated with severity and inhospital mortality in patients with COVID-19. There was no significant difference between the risk factors assessed (age, sex, arterial hypertension, diabetes mellitus, and chronic obstructive pulmonary disease) regarding severity and mortality. Obesity (BMI ≥ 30) indicated a significant difference in disease severity, with a higher prevalence among noncritical patients (57.2%) compared to critical patients (29.1%) ($P = 0.0009$). In the univariate logistic regression for the mortality analysis, only heart disease showed a significant difference among the other comorbidities (Table 1).

BMI analysis showed that 101 (50.5%) patients had obesity (BMI > 30 kg/m^2), with 42 (21%) with severe obesity (BMI ≥ 35 kg/m^2), while only 28 (14%) of the patients had a BMI lower than 25 kg/m^2 and 71 patients were overweight (35.5%). The median SAT area was 161.4 cm^2 and the median VAT area was 127 cm^2, with a median VAT/SAT ratio of 0.83. The median MA was 89.6 cm^2 and the median VAT/MA ratio was 1.47 (Table 2).

Clinical outcomes

Regarding complications, patients admitted to the ICU or who progressed to a state of shock of any etiology or who required mechanical ventilation during hospitalization had high inhospital mortality. We did not find any significant difference between the scores assessed on patient admission (NEWS2, q-SOFA, and CT COVID19) and mortality, and disease severity (Table 1). In Spearman's correlation analyses, leptin showed a directly proportional relationship in descending order with SAT, BMI, VAT/MA, and VAT and inversely proportional relationship with the VAT/SAT ratio. The greatest correlation between variables was between BMI vs SAT ($r = 0.664$) and BMI vs MA ($r = 0.435$) (Fig. 2A).

Regarding the tomographic variables, in the evaluation by the Mann–Whitney test, the MA was significantly reduced in critical patients compared to noncritical patients, and VAT/SAT and VAT/MA ratios were higher in critically ill patients. Regarding the laboratory variables, D-dimer, hs-CRP, LDH, ALT, leukocytes, neutrophils, and NRL also showed a significant difference in the disease severity. However, the variables leptin, IL6, albumin, SAT, and creatinine showed no significant difference (Table 2).

Supplementary Table 1 summarizes the comparison between patients with different body compositions (obesity and MA < 92 cm^2). The comparison showed that age, VAT, SAT, VAT/SAT, MA, VAT/MA, leptin, D-dimer,

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Table 1 Demographic and clinical characteristics of the cohort in noncritical and critical patients and their association with mortality.

Variables	Total (n = 200)	Severity			Univariate logistic regression		
					Mortality		
		Noncritical (n = 152)	Critical (n = 48)	P value	OR	95% CI	P value
Median age (years) (IQR)	62 (50–74)	61.5 (49–73.75)	64.5 (50.5–76)	0.190	1.021	0.993–1.050	0.139
Age > 60 years, n (%)	109 (54.5)	78 (51.3)	31 (64.5)	0.134	1.710	0.765–4.030	0.201
Male, n (%)	113 (56.5)	90 (59.2)	23 (47.9)	0.1845	0.678	0.305–1.499	0.335
Comorbidities							
Hypertension, n (%)	133 (66.5)	97 (63.8)	36 (75)	0.165	1.383	0.596–3.495	0.529
Diabetes mellitus, n (%)	97 (48.5)	69 (45.3)	28 (58.3)	0.137	1.611	0.730–3.653	0.241
Obesity, n (%)	101 (50.5)	87 (57.2)	14 (29.1)	0.0009	0.892	0.247–2.539	0.844
Heart disease, n (%)	26 (13)	23 (15.1)	3 (6.2)	0.141	0.423	0.096–1.296	0.017
Neoplasm, n (%)	2 (1)	1 (0.6)	1 (2.0)	0.423	6.071	0.235–156.4	0.206
Chronic lung disease, n (%)	10 (5)	9 (5.9)	1 (2.0)	0.45	0.642	0.034–3.623	0.687
Complications							
Use of vasoactive drugs, n (%)	21 (10.5)	1 (0.6)	20 (41.6)	<0.0001	59.1	18.7–232	<0.0001
Ventilation, n (%)	24 (12)	0 (0)	24 (50)	<0.0001	265	63–1890	<0.0001
Admission to the ICU, n (%)	44 (22)	0 (0)	59 (89.4)	<0.0001	50	17.2–184	<0.0001
Length of stay in the hospital (days), median (IQR)	6 (4–10)	5 (4–7)	11 (7.25–17)	<0.0001	1.146	1.087–1216	<0.0001
Scores systems							
NEWS2 score, median (IQR)	6 (5–7)	6 (5–7)	5 (5–7)	0.631	1.055	0.857–1.298	0.609
q-SOFA score, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.111	1.831	0.781–4.590	0.177
CT COVID score, median (IQR)	20 (15–20)	20 (15–20)	20 (15–20)	0.176	1.069	0.989–1.177	0.127

The Mann–Whitney test was performed for continuous variables (age, NEWS2, q-SOFA, and CT COVID-19 score), while Fisher's exact test was performed for all other variables.

COVID, coronavirus disease; ICU, intensive care unit; IQR: interquartile range; NEWS2, National Early Warning Score 2; OR, odds ratio; q-SOFA, Quick Sepsis-Related Organ Failure Assessment.

ALT, and creatinine were significantly different between groups. A bar graph of the same data also illustrates these points; the mortality rate was higher in the sarcopenic group (MA < 92 cm^2) without obesity than in the sarcopenic obesity group (28.2% vs 12.5%, $P=0.0004$) (Fig. 2B).

Kaplan–Meier curves showed that patients with age > 70 years, MA < 92 cm^2, and without obesity (BMI < 30) had lower survival rate (hazard ratio (HR) 2.3–9.66; P < 0.0006) than the other groups. The group with the best survival rate was patients with obesity with MA > 92 cm^2 and age < 70 years (Fig. 3A and B).

Next, Figure 4A shows VAT, SAT, MA, VAT/MA, and VAT/SAT results among survivor and nonsurvivor patients. The mortality rates were bubble plotted considering MA and VAT. Notably, survival and shorter length of stay segregated with high MA and low VAT, whereas mortality and longer length of stay segregated with high VAT and low MA (Fig. 4B).

We analyzed the potential of these tomographic and laboratory variables as predictors of mortality due to COVID-19, using the ROC curve (Fig. 4C and Table 3). The variables that were individually shown to be potential markers of mortality in descending order (P < 0.05) were VAT/MA, MA, hs-CRP, number of neutrophils, VAT/SAT ratio, NLR, D-dimer, LDH, VAT, and age. The variable with the highest sensitivity was MA (0.86), while the VAT/SAT ratio had the highest specificity (0.86). Next, using the cutoff value for each parameter, we calculated the OR of mortality using the Fisher's exact test. The cutoff points for MA < 92 cm^2 (OR: 6.17), VAT/MA ratio > 2 cm^2 (OR: 6.84), hs-CRP > 70 mg/dL (OR: 4.48), and number of neutrophils > 8185 (OR: 4.33) represented the highest relative risks for inhospital mortality in our study (Table 3).

We next used univariate and multivariate regression analyses (adjusted by other variables) to calculate the mortality OR by using cutoff values obtained from the ROC curve (Table 3). Patients with MA < 92 cm^2 during

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Table 2 Tomographic and laboratory variables evaluated in noncritical and critical patients and their association with mortality.

	Mann–Whitney test							Univariate logistic regression		
	Severity							Mortality		
	Total		Noncritical		Critical					
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*P*	OR	95% CI	*P*
BMI	200	30.0 (26.8–34.3)	152	30.6 (27.2–34.5)	48	28.5 (26–31.1)	0.0265	0.97	0.914–1.036	0.094
VAT (cm^2)	200	127 (85.8–180.5)	152	124.6 (81.2–178.9)	48	151.4 (105.5–190.7)	0.154	1.005	0.999–1.010	0.034
SAT (cm^2)	200	161.4 (102.4–217.7)	152	163.7 (102.9–218.5)	48	136.2 (100.6–205.5)	0.349	0.997	0.992–1.002	0.201
VAT/SAT	200	0.83 (0.54–1.29)	152	0.78 (0.48–1.27)	48	1.01 (0.67–1.41)	0.0354	1.998	1.191–3.336	0.0055
MA (cm^2)	200	89.6 (75.5–112)	152	91.6 (76.9–115.8)	48	83 (69.8– 101.3)	0.025	0.928	0.900–0.952	<0.0001
VAT/MA	200	1.47 (0.96–1.96)	152	1.32 (0.92–1.89)	48	1.73 (1.39–2.18)	0.0033	5.213	2.890–10.43	<0.0001
IL6 (pg/mL)	199	54.1 (24.1–104.3)	151	54.1 (23–98.4)	48	55 (27.2–124.2)	0.5715	0.999	0.998–1.001	0.334
D-dimer (ng/mL)	198	795.4 (498 – 1682)	152	728 (485.1– 1359)	46	1410 (609.9–3596)	0.0038	1.000	1.000–1.000	0.0223
Leptin (ng/mL)	200	4.6 (1.8–9.3)	152	4.7 (1.8–9)	48	4.3 (1.4–9.5)	0.8179	0.966	0.897–1.021	0.625
LDH (U/L)	190	735 (559.5–1006)	144	702.5 (550.3–959.3)	46	822.5 (580.8–1169)	0.0243	1.001	1.000–1.002	0.03
hs-CRP (mg/dL)	184	86.1 (37.8–150.8)	138	71 (34–139.2)	46	139.5 (49.1–184.1)	0.0104	1.011	1.005–1.018	0.0014
ALT (U/L)	195	61 (38.6–101)	148	67 (41.0–101.8)	47	49 (23.0–94.0)	0.0413	0.993	0.984–1.001	0.04
AST (U/L)	195	54 (37.0–80.0)	148	54 (37.0–81.5)	47	48 (36.0–77.0)	0.6198	0.995	0.985–1.003	0.400
Neutrophils ($\times 10^3$cells/μL)	200	7199 (5261–9497)	152	6746 (5162–8938)	48	8617 (6399–11321)	0.006	1.000	1.000–1.000	0.0009
NLR	200	9.11 (6.02–14.6)	152	8.63 (5.6–14.2)	48	9.5 (7.98–17.6)	0.0743	1.055	1.002–1.110	0.0061
Albumin (mg/dL)	200	3.3 (3.0–3.7)	152	3.3 (3.0–3.7)	48	3.3 (2.7–3.6)	0.2056	0.526	0.234–1.143	0.221
Creatinine (mg/dL)	195	1.1 (0.88–1.35)	150	1.1 (0.9–1.35)	45	1.06 (0.8–1.35)	0.4084	1.009	0.682–1.191	0.933

Mann–Whitney test and Univariate logistic regression (mortality) analysis were performed for all variables.
ALT, alanine transaminase; AST, aspartate transaminase; hs-CRP, high-sensitivity C-reactive protein; IL6, interleukin-6; IQR, interquartile range; LDH, lactate dehydrogenase; MA, muscle area; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; SAT, s.c. adipose tissue area; VAT, visceral adipose tissue area.

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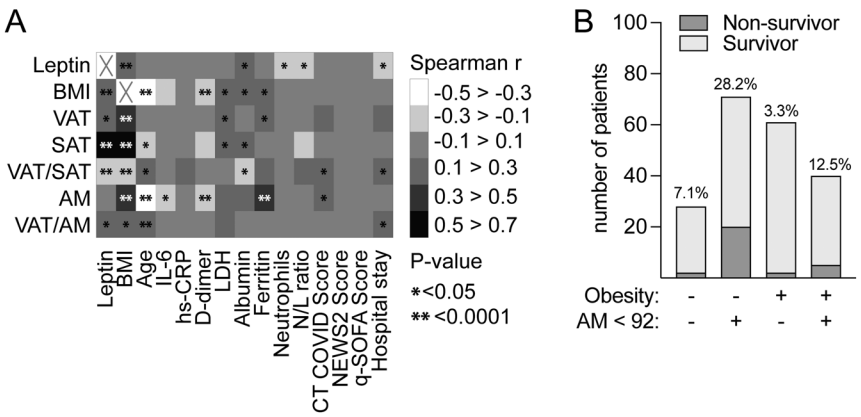

Figure 2
Tomographic and laboratory variables of 200 COVID-19 hospitalized patients collected during the first 48 h of admission (Spearman's correlation and bar chart). (A) Spearman's correlation. (B) Bar chart depicting sample number with (+) and without (–) the parameter below the cutoff (BMI > 30, MA < 92) in patients with COVID-19 (survivors vs nonsurvivors) and highlighting the proportion of nonsurvivor. Statistics used: Spearman's correlation. COVID-19, coronavirus disease-19; hs-CRP, high-sensitivity C-reactive protein; IL6, interleukin-6; LDH, lactate dehydrogenase; MA, muscle area; NEWS2, National Early Warning Score 2; NLR, neutrophil–lymphocyte ratio; q-SOFA, Quick Sepsis-Related Organ Failure Assessment; SAT, s.c. adipose tissue area; VAT, visceral adipose tissue area.

admission were associated with a 6.17-fold increase in the odds of mortality (95% CI: 2.27–21, $P=0.0011$) in univariate regression and 7.94 times (95% CI: 2.08–38.6, $P=0.0046$) in the multivariate regression. Patients with a VAT/MA ratio >2 cm^2 were associated with 6.84 times (95% CI: 2.99–16, $P < 0.0001$) and 13.9 times (95% CI: 4.4–52, $P < 0.0001$) of increased chance of lethality in univariate and multivariate logistic regression analyses, respectively (Table 4).

Discussion

The COVID-19 pandemic presented an unprecedented challenge to the worldwide health-care system. With the scarcity of resources in the health area, the early identification of risk factors associated with the severity and mortality of COVID-19 is crucial. To date, this is the largest prospective study of patients hospitalized with COVID-19 in which body composition, fat distribution, and serum leptin levels were evaluated and correlated.

In our study, VAT and MA were the main parameters related to mortality from COVID-19, and the SAT/MA ratio corresponded to the best variable in the study, with an area of 0.74 in the ROC curve (Table 3). SAT in isolation was not related to mortality, and BMI presented a low area of the ROC curve (0.59). Therefore, patients who had an SAT/MA ratio > 2.0 had a relative risk of inhospital death increased to 6.84 times, and when adjusted for age, sex, leptin, and other laboratory tests, the risk increased to 13.9 (Table 4).

The association of VAT and MA with worse outcomes is not unexpected, based on previous research on death (4, 5), but what our study found was a very significant OR, which was a better predictor than several other more recognized markers of severity, such as age and inflammatory markers. Indeed, low MA, and sarcopenia itself, could be a marker of vulnerability and aging, but even after adjustment of confounders, such as age itself, its relation remains highly significant. As such, one hypothesis raised by our results is that age-related worse prognosis in COVID-19 could be mediated by sarcopenia. Although age is an objective measure, different life-course stressors could mean that individuals with the same biological age will have extremely different health risks, especially in low- and middle-income countries, like Brazil (25). As such, although much more difficult to measure, low MA could

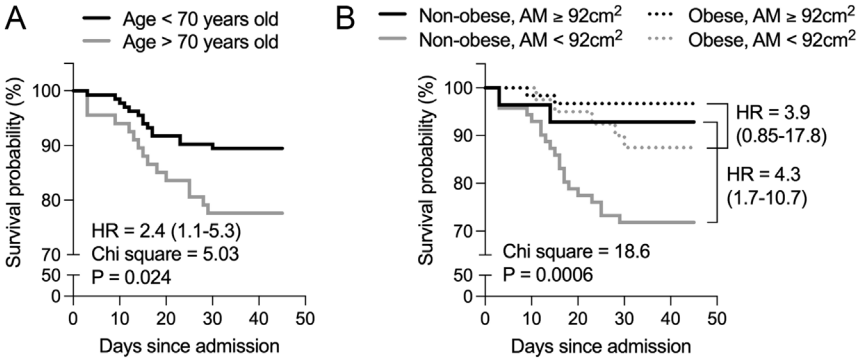

Figure 3
Kaplan–Meier curves for predicting mortality in patients with COVID-19 (age, obesity, and MA < 92 cm^2). COVID-19, coronavirus disease-19; HR, hazard ratio; MA, muscle area.

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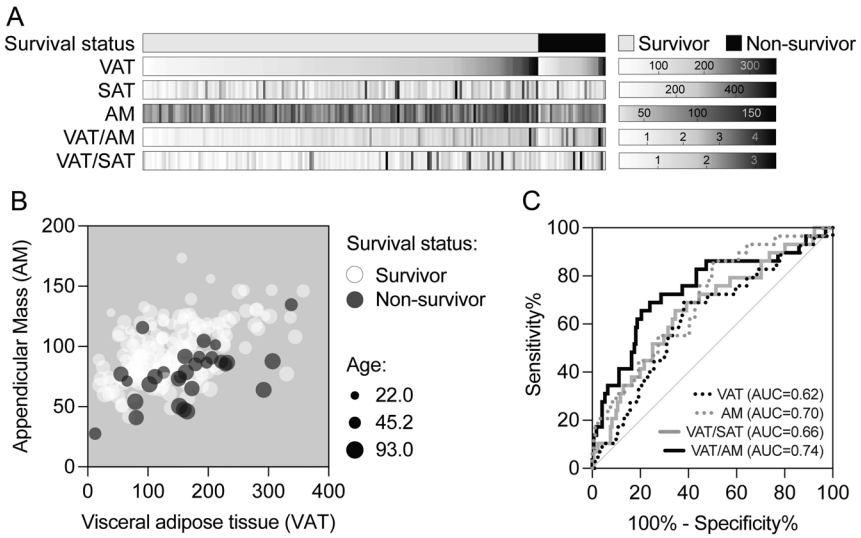

Figure 4
Tomographic and laboratory variables of 200 COVID-19 hospitalized patients collected during the first 48 h of admission. (A) Heatmap showing tomographic variable (VAT, SAT, MA, VAT/MA, and VAT/SAT) classification below, within, and above normal range in patients with COVID-19 (survivors vs nonsurvivors). (B) Bubble plot displaying the MA and VAT in patients with COVID-19 (survivors vs nonsurvivors). (C) Mortality risk ROC curve and AUC score with parameters of VAT, MA, VAT/MA, VAT/SAT. COVID-19, coronavirus disease-19; MA, muscle area; ROC, receiver operating characteristic; SAT, s.c. adipose tissue area; VAT, visceral adipose tissue area.

be a better predictor of overall health and outcomes than age itself.

Visceral fat is associated with insulin resistance, worse metabolic health, and systemic inflammation; many authors have discussed that fat distribution itself would be a better marker of worse outcomes in COVID-19, and research helps to corroborate that hypothesis (26, 27, 28). In the Kaplan–Meier curve, we observed in our study that the group of patients without obesity (BMI < 30) and with MA < 92 cm^2 had the highest inhospital mortality with a risk ratio of 9.66 regarding patients with obesity and muscle mass > 92 cm^2, which corresponded to the group with the lowest mortality (Fig. 3).

Interestingly, in our study, obesity was a protective risk factor for disease severity and neutral for mortality (Table 1), which suggests that weight itself is a poor marker of overall health status. Nonetheless, the prevalence of obesity was 50.5% (Table 1) in our cohort, which is almost two and a half times higher than in the general population of Brazil (20.3%) (29). The prevalence of obesity was higher in noncritical patients (45.3%) than in critically ill patients (29.1%) ($P=0.0009$) (Table 1). Moreover, the Kaplan–Meier curve (Fig. 3B) curve showed that patients with obesity and low muscle mass have higher mortality than patients with obesity and normal muscle mass (HR = 3.9, $P=0.0006$). Low muscle mass was more important than comorbidities associated with COVID-19 in hospitalized patients in our

Table 3 Variables analyzed as potential mortality biomarkers – ROC curve.

Variables	ROC curve		Cutoff characterization				Fisher's exact test		
	AUC	95% CI	Cutoff	Sensitivity	Specificity	*P* value	OR	95% CI	*P* value
Age	0.58	0.47– 0.69	>70	0.51	0.71	0.143	2.45	1.14–5.31	0.0329
BMI	0.59	0.48–0.70	<30	0.75	0.55	0.094	3.83	1.54–9.99	0.0024
VAT	0.62	0.51–0.73	>150	0.69	0.62	0.034	3.44	1.47–8.41	0.0041
SAT	0.57	0.46–0.68	<145	0.69	0.58	0.203	2.74	1.19–6.12	0.015
VAT/SAT	0.66	0.55–0. 77	>1.57	0.34	0.86	0.005	3.38	1.36–8.12	0.011
MA	0.69	0.59–0.79	<92	0.86	0.49	0.0007	6.17	2.15–16.95	0.0002
VAT/MA	0.74	0.63–0.85	>2.0	0.62	0.80	<0.0001	6.84	3.01–15.22	<0.0001
Leptin	0.52	0.41–0.63	<4.15	0.51	0.53	0.62	1.24	0.59–2.65	0.68
Albumin (g/dL)	0.57	0.45–0.69	<2.85	0.34	0.84	0.22	2.93	1.20–6.86	0.018
hs-CRP (mg/dL)	0.69	0.57–0.80	>70	0.82	0.49	0.0014	4.48	1.69–11.21	0.0019
LDH (U/L)	0.63	0.50–0.75	>714	0.78	0.50	0.03	3.45	1.39–8.67	0.011
D-dimer (ng/mL)	0.63	0.51–0.74	>946	0.64	0.60	0.02	2.63	1.12–5.95	0.023
IL6 (pg/mL)	0.55	0.43–0.67	>130	0.34	0.85	0.33	3.07	1.25–7.24	0.015
Neutrophils	0.69	0.59–0.79	>8.185	0.69	0.66	0.0007	4.33	1.83–10.62	0.0007
NRL	0.65	0.55–0.76	>15	0.41	0.83	0.006	3.45	1.50–7.79	0.0052

ROC curve analysis and Fisher's exact test were performed for all variables.
AUC, area under the curve; hs-CRP, high-sensitivity C-reactive protein; IL6, interleukin-6; LDH, lactate dehydrogenase; MA, muscle area; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; ROC, receiver operating characteristic; SAT, s.c. adipose tissue; VAT, visceral adipose tissue.

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Table 4 Univariate and multivariate regression analyses between variables.

Variable	Univariate logistic regression			Multiunivariate logistic regression			Multiunivariate logistic regression		
	Mortality			Mortality[a]			Mortality[b]		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age > 70 years	2.45	1.10–5.50	0.027	2.51	1.12–5.67	0.024	–	–	–
VAT > 150 cm^2	3.44	1.52–8.38	0.01	3.54	1.55–8.66	0.0031	3.32	1.46–8.11	0.005
SAT < 145 cm^2	2.74	1.22–6.47	0.01	2.62	1.10–6.64	0.03	2.56	1.13–6.11	0.026
VAT/SAT > 1.57	3.38	1.36–8.10	0.006	3.19	1.27–7.74	0.011	3.12	1.24–7.56	0.012
MA < 92 cm^2	6.17	2.27–21	0.0011	6.52	2.39–22.9	0.0009	6.06	2.1–22.2	0.002
VAT/MA > 2.0	6.84	2.99–16	<0.0001	7.4	3.19–18	<0.0001	6.48	2.78–15.7	<0.0001

Multiunivariate logistic regression			
	Mortality[c]		
	OR	95% CI	*P* value
	1.85	0.68–4.98	0.21
	6.15	1.96–21.88	0.0018
	2.89	1.03–8.58	0.046
	4.47	1.21–17.26	0.02
	7.94	2.08–38.6	0.0046
	13.9	4.4–52	< 0.0001

[a]Adjusted for leptin; [b]Adjusted for age; [c]Adjusted for age, sex, leptin, neutrophil (×10^3cells/μL), NLR, albumin, hs-CRP, LDH, D-dimer, and IL6.
hs-CRP, high-sensitivity C-reactive protein; IL, interleukin-6; LDH, lactate dehydrogenase; MA, muscle area; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; SAT, s.c. adipose tissue area; VAT, visceral adipose tissue area.

region. These findings suggest the importance of lower muscle mass compared to BMI obesity and that obesity is indeed a risk factor for hospitalizations, as many other studies have shown.

Recently, in a meta-analysis with 75 studies evaluated (mostly retrospective studies), it was found that patients with obesity were more likely to have unfavorable outcomes regarding COVID-19. Obesity significantly increased the chance of admission to the ICU by 74% and increased the chance of death by 48% (4). However, in the same meta-analysis, the authors cited eight studies that showed that individuals with obesity had a lower risk of inhospital mortality; this could be attributed to differences in the overall characteristics of the population (age, comorbidities, and access to health), as well as in criteria for hospitalization. Further studies to analyze the true context of obesity and its peculiarities as a risk factor in morbidity and mortality from COVID-19 are essential, especially in food transition developing countries.

However, only a few studies analyzed and correlated body composition with COVID-19 severity and mortality. A retrospective study conducted in China with 143 patients hospitalized with COVID-19 showed visceral adiposity (OR: 2.47, $P=0.040$) and high i.m. fat concentration (OR: 11.90, $P < 0.001$) as independent risk factors for critical illness (30). Recently, Pranata and coworkers (2020) evaluated five studies (539 patients) in a meta-analysis and demonstrated that patients with severe COVID-19 had higher VAT values and total fat tissue area, but not SAT, in relation to patients with nonsevere COVID-19 (31).

In our study, leptin was not associated with severity and inhospital mortality due to COVID-19. Leptin was mainly correlated with SAT and BMI and, inversely, with the length of hospital stay. Leptin is a keystone in regulating the metabolism–immune system interaction. Previous studies have suggested that leptin increases the production of T-helper 1 (Th1) inflammatory cytokines and suppresses Th2 anti-inflammatory cytokines by T lymphocytes (32).

In the literature review, only four studies evaluated leptin levels in patients with COVID-19 (33, 34, 35, 36). However, the four studies had major limitations, such as the small number of patients. In our study, leptin was not statistically correlated with IL6 and hs-CRP. Similar to leptin, IL6 was not directly related to inhospital mortality (Tables 2 and 3). Recently, a review and meta-analysis questioned some important points about the pathogenesis of COVID-19. Elevations of inflammatory cytokines (mainly IL6) in critically ill patients with COVID-19 are considerably lower than those reported in patients with acute respiratory distress syndrome and are

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nonrelated to COVID-19. However, several noncytokine biomarkers associated with chronic inflammation or endothelial dysfunction, such as hs-CRP, D-dimer, and ferritin, are higher in patients with COVID-19 than in patients with other serious nonCOVID-19 diseases (37). The major limitations of our study were (i) the absence of a healthy control group or patients with mild symptoms to correlate with the researched results and (ii) the lack of standardization in the imaging techniques (thoracic CT) adopted in our study to distinguish the different types of tissues analyzed (fat and muscle). Additionally, it is necessary to standardize the index or cutoff points for the diagnosis of sarcopenia and visceral obesity, based on sufficient evidence and international consensus.

In summary, to date, this work represents a prospective study with the largest number of hospitalized patients that linked body composition and leptin levels with mortality and other biomarkers related to COVID-19. We conclude that low muscle mass and increased fat mass, especially visceral, were better predictors of inhospital COVID-19 mortality than BMI, as well as leptin.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-22-0290.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

1 Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM & Al-Nasser AD. Sars-cov-2 and coronavirus disease 2019: what we know so far. *Pathogens* 2020 **9** 231. (https://doi.org/10.3390/pathogens9030231)

2 Park M, Cook AR, Lim JT, Sun Y & Dickens BL. A systematic review of COVID-19 epidemiology based on current evidence. *Journal of Clinical Medicine* 2020 **9** 967. (https://doi.org/10.3390/jcm9040967)

3 Ye Q, Wang B, Mao J, Fu J, Shang S, Shu Q & Zhang T. Epidemiological analysis of COVID-19 and practical experience from China. *Journal of Medical Virology* 2020 **92** 755–769. (https://doi.org/10.1002/jmv.25813)

4 Popkin BM, Du S, Green WD, Beck MA, Algaith T, Herbst CH, Alsukait RF, Alluhidan M, Alazemi N & Shekar M. Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships. *Obesity Reviews* 2020 **21** e13128. (https://doi.org/10.1111/OBR.13128)

5 Halpern B, Louzada MLDC, Aschner P, Gerchman F, Brajkovich I, Faria-Neto JR, Polanco FE, Montero J, Juliá SMM, Lotufo PA, *et al.* Obesity and COVID-19 in Latin America: a tragedy of two pandemics – official document of the Latin American Federation of Obesity Societies. *Obesity Reviews* 2021 **22** e13165. (https://doi.org/10.1111/OBR.13165)

6 Fan Z, Shi Y, Huang G, Hou D & Liu J. Long-term changes in body composition and their relationships with cardiometabolic risk factors: a population-based cohort study. *PLoS ONE* 2021 **16** e0251486. (https://doi.org/10.1371/journal.pone.0251486)

7 Elffers TW, de Mutsert R, Lamb HJ, de Roos A, Willems van Dijk K, Rosendaal FR, Jukema JW & Trompet S. Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women. *PLoS ONE* 2017 **12** e0185403. (https://doi.org/10.1371/JOURNAL.PONE.0185403)

8 Watanabe M, Caruso D, Tuccinardi D, Risi R, Zerunian M, Polici M, Pucciarelli F, Tarallo M, Strigari L, Manfrini S, *et al.* Visceral fat shows the strongest association with the need of intensive care in patients with COVID-19. *Metabolism: Clinical and Experimental* 2020 **111** 154319. (https://doi.org/10.1016/J.METABOL.2020.154319)

9 Silverio R, Gonçalves DC, Andrade MF & Seelaender M. Coronavirus disease 2019 (COVID-19) and nutritional status: the missing link? *Advances in Nutrition* 2021 **12** 682–692. (https://doi.org/10.1093/ADVANCES/NMAA125)

10 Nezameddin R, Itani L, Kreidieh D, el Masri D, Tannir H & Ghoch ME. Understanding sarcopenic obesity in terms of definition and health consequences: a clinical review. *Current Diabetes Reviews* 2020 **16** 957–961. (https://doi.org/10.2174/1573399816666200109091449)

11 Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M, *et al.* High prevalence of obesity in severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity* 2020 **28** 1195–1199. (https://doi.org/10.1002/oby.22831)

12 Huang Y, Lu Y, Huang YM, Wang M, Ling W, Sui Y & Zhao HL. Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism: Clinical and Experimental* 2020 **113** 154378. (https://doi.org/10.1016/j.metabol.2020.154378)

13 Molfino A, Imbimbo G, Rizzo V, Muscaritoli M & Alampi D. The link between nutritional status and outcomes in COVID-19 patients in ICU: is obesity or sarcopenia the real problem? *European Journal of Internal Medicine* 2021 **91** 93–95. (https://doi.org/10.1016/J.EJIM.2021.06.028)

14 McGovern J, Dolan R, Richards C, Laird BJ, McMillan DC & Maguire D. Relation between body composition, systemic inflammatory response, and clinical outcomes in patients admitted to an urban teaching hospital with COVID-19. *Journal of Nutrition* 2021 **151** 2236–2244. (https://doi.org/10.1093/JN/NXAB142)

15 Petersen A, Bressem K, Albrecht J, Thieß HM, Vahldiek J, Hamm B, Makowski MR, Niehues A, Niehues SM & Adams LC. The role of visceral adiposity in the severity of COVID-19: highlights from a unicenter cross-sectional pilot study in Germany. *Metabolism: Clinical and Experimental* 2020 **110** 154317. (https://doi.org/10.1016/J.METABOL.2020.154317)

16 Gao M, Wang Q, Piernas C, Astbury NM, Jebb SA, Holmes MV & Aveyard P. Associations between body composition, fat distribution and metabolic consequences of excess adiposity with severe COVID-19 outcomes: observational study and Mendelian randomisation analysis. *International Journal of Obesity* 2022 **46** 943–950. (https://doi.org/10.1038/s41366-021-01054-3)

17 Lockhart SM & O'Rahilly S. When two pandemics meet: why is obesity associated with increased COVID-19 mortality? *Medicine* 2020 **1** 33–42. (https://doi.org/10.1016/J.MEDJ.2020.06.005)

18 Ponti F, Santoro A, Mercatelli D, Gasperini C, Conte M, Martucci M, Sangiorgi L, Franceschi C & Bazzocchi A. Aging and imaging assessment

of body composition: from fat to facts. *Frontiers in Endocrinology* 2019 **10** 861. (https://doi.org/10.3389/FENDO.2019.00861)
19 Zhang F, Basinski MB, Beals JM, Briggs SL, Churgay LM, Clawson DK, DiMarchi RD, Furman TC, Hale JE, Hsiung HM, *et al.* Crystal structure of the obese protein leptin-E100. *Nature* 1997 **387** 206–209. (https://doi.org/10.1038/387206a0)
20 Philbrick KA, Wong CP, Branscum AJ, Turner RT & Iwaniec UT. Leptin stimulates bone formation in ob/ob mice at doses having minimal impact on energy metabolism. *Journal of Endocrinology* 2017 **232** 461–474. (https://doi.org/10.1530/JOE-16-0484)
21 Zhang AJX, To KKW, Li C, Lau CCY, Poon VKM, Chan CCS, Zheng BJ, Hung IFN, Lam KSL, Xu A, *et al.* Leptin mediates the pathogenesis of severe 2009 pandemic influenza A(H1N1) infection associated with cytokine dysregulation in mice with diet-induced obesity. *Journal of Infectious Diseases* 2013 **207** 1270–1280. (https://doi.org/10.1093/infdis/jit031)
22 Beltrão FEde L, Beltrão DCde A, Carvalhal G, Beltrão FEde L, Brito Ada S, Capistrano KHR da, Bastos IH de A, Hecht F, Daltro CHC, Bianco AC, *et al.* Thyroid hormone levels during hospital admission inform disease severity and mortality in COVID-19 patients. *Thyroid* 2021 **31** 1639–1649. (https://doi.org/10.1089/THY.2021.0225/ASSET/IMAGES/MEDIUM/THY.2021.0225_FIGURE1.JPG)
23 Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, *et al.* Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19). *Radiology* 2020 **295** 715–721. (https://doi.org/10.1148/radiol.2020200370)
24 Nemec U, Heidinger B, Sokas C, Chu L & Eisenberg RL. Diagnosing sarcopenia on thoracic computed tomography: quantitative assessment of skeletal muscle mass in patients undergoing transcatheter aortic valve replacement. *Academic Radiology* 2017 **24** 1154–1161. (https://doi.org/10.1016/J.ACRA.2017.02.008)
25 Ford ND, Patel SA & Narayan KMV. Obesity in low- and middle-income countries: burden, drivers, and emerging challenges. *Annual Review of Public Health* 2017 **38** 145–164. (https://doi.org/10.1146/ANNUREV-PUBLHEALTH-031816-044604)
26 Sattar N, McInnes IB & McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation* 2020 **142** 4–6. (https://doi.org/10.1161/CIRCULATIONAHA.120.047659)
27 Stefan N, Birkenfeld AL, Schulze MB & Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. *Nature Reviews: Endocrinology* 2020 **16** 341–342. (https://doi.org/10.1038/s41574-020-0364-6)
28 Drucker DJ. Diabetes, obesity, metabolism, and SARS-CoV-2 infection: the end of the beginning. *Cell Metabolism* 2021 **33** 479–498. (https://doi.org/10.1016/J.CMET.2021.01.016)
29 Oliveira MM de, Stopa SR, Gouvea ECDP, Ferreira KRD, Santos Rde O, Valença Neto Pda F, Macário EM & Sardinha LMV. Temporal trend of overweight and obesity prevalence among Brazilian adults, according to sociodemographic characteristics, 2006-2019. *Epidemiologia e Serviços de Saúde* 2021 **30** e2020294. (https://doi.org/10.1590/S1679-49742021000100008)
30 Yang Y, Ding L, Zou X, Shen Y, Hu D, Hu X, Li Z, Kamel IR & Hu X. Visceral adiposity and high intramuscular fat deposition independently predict critical illness in patients with Sars-COV-2. *Obesity* 2020 **28** 2040–2048. (https://doi.org/10.1002/oby.22971)
31 Pranata R, Lim MA, Huang I, Yonas E, Henrina J, Vania R, Lukito AA, Nasution SA, Alwi I & Siswanto BB. Visceral adiposity, subcutaneous adiposity, and severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *Clinical Nutrition ESPEN* 2021 **43** 163–168. (https://doi.org/10.1016/J.CLNESP.2021.04.001)
32 Francisco V, Pino J, Campos-Cabaleiro V, Ruiz-Fernández C, Mera A, Gonzalez-Gay MA, Gómez R & Gualillo O. Obesity, fat mass and immune system: role for leptin. *Frontiers in Physiology* 2018 **9** 640. (https://doi.org/10.3389/fphys.2018.00640)
33 Voort PHJ van der, Moser J, Zandstra DF, Muller Kobold AC, Knoester M, Calkhoven CF, Hamming I & Meurs M van. Leptin levels in SARS-CoV-2 infection related respiratory failure: a cross-sectional study and a pathophysiological framework on the role of fat tissue. *Heliyon* 2020 **6** e04696. (https://doi.org/10.1016/j.heliyon.2020.e04696)
34 Blot M, David Masson, Nguyen M, Bourredjem A, LYMPHONIE Study Group, Binquet C & Piroth L. Are adipokines the missing link between obesity, immune response, and outcomes in severe COVID-19? *International Journal of Obesity* 2021 **45** 2126–2131. (https://doi.org/10.1038/S41366-021-00868-5)
35 Filippo L di, Lorenzo R de, Sciorati C, Capobianco A, Lorè NI, Giustina A, Manfredi AA, Rovere-Querini P & Conte C. Adiponectin to leptin ratio reflects inflammatory burden and survival in COVID-19. *Diabetes and Metabolism* 2021 **47** 101268. (https://doi.org/10.1016/J.DIABET.2021.101268)
36 Wang J, Xu Y, Zhang X, Wang S, Peng Z, Guo J, Jiang H, Liu J, Xie Y, Wang J, *et al.* Leptin correlates with monocytes activation and severe condition in COVID-19 patients. *Journal of Leukocyte Biology* 2021 **110** 9–20. (https://doi.org/10.1002/JLB.5HI1020-704R)
37 Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, *et al.* Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet: Respiratory Medicine* 2020 **8** 1233–1244. (https://doi.org/10.1016/S2213-2600(20)30404-5)

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