Sarcopenia, myosteatosis and inflammation are independent prognostic factors of SARS-CoV-2 pneumonia patients admitted to the ICU

Romain Chauvot de Beauchene, Bertrand Souweine, Benjamin Bonnet, Bertrand Evrard, Yves Boirie, Lucie Cassagnes, Claire Dupuis

scientific reports

Check for updates

OPEN

Sarcopenia, myosteatosis and inflammation are independent prognostic factors of SARS-CoV-2 pneumonia patients admitted to the ICU

Romain Chauvot de Beauchene[1], Bertrand Souweine[2,3], Benjamin Bonnet[4,5], Bertrand Evrard[4,5], Yves Boirie[6,7], Lucie Cassagnes[1,7] & Claire Dupuis[2,7,8]✉

The aims of our study were to assess the correlations between sarcopenia and myosteatosis assessed by CT-scan at T4 and/or L3 levels and inflammation in critically ill COVID patients on ICU admission, and their respective prognostic value on day 90 death (D90-death). It is a retrospective monocentric study. Sarcopenia was defined by skeletal muscle cross sectional surface area (CSA) and myosteatosis by skeletal muscle density (SMD) at L3 and T4 levels. Inflammatory biomarkers were collected on ICU admission. Of the 239 patients, 74 died by D90; 66.6% get sarcopenia on ICU admission. CSA at T4 level was an independent risk factor for D90-death (1.66[1.03; 2.66]; $p = 0.04$), as were procalcitonin (2.03[1.2; 3.43]; $p = 0.01$) and IL-6 levels (1.56[0.96; 2.54]; $p = 0.07$). In addition, we found correlation factors of 0.79 ($p < 0.01$) between SMD at T4 and L3 levels, and a correlation factor of 0.64 ($p < 0.01$) between CSA at T4 and L3 levels.These results indicate a poorer prognosis following a decrease in muscle surface area, a decrease in density, and an increase in inflammatory biomarkers such as Il6. It also suggests that incorporating indices of sarcopenia with inflammatory biomarkers may improve prognostic accuracy.

Keywords COVID 19, Inflammation, Chest CT-scan, Sarcopenia, Low muscle mass, Critical illness, Outcome

Abbreviations

AI	Artificial intelligence
ARDS	Acute respiratory distress syndrome
AUC	Area under curve
BMI	Body mass index
BNP	Brain natriuretic peptide
CHU	University Hospital Centre
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSA	skeletal surface Cross-Sectional Area
CRP	C-reactive protein
HAS	Haute Autorité de Santé
HTA	Hypertension
HU	Hounsfield unit

[1]Radiology Department, Clermont-Ferrand University hospital, Clermont-Ferrand, France. [2]Intensive Care Department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France. [3]CNRS, LMGE, Clermont Auvergne University, Clermont-Ferrand 63000, France. [4]Immunology Department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France. [5]Laboratory of Immunology, ECREIN, UMR1019 UNH, UFR Médecine de Clermont-Ferrand, Clermont Auvergne University, Clermont-Ferrand, France. [6]Clinical nutrition department, Clermont-Ferrand University hospital, Clermont-Ferrand, France. [7]Unité de Nutrition Humaine, INRAe, CRNH Auvergne, Clermont Auvergne University, Clermont Ferrand 63000, France. [8]Service de Médecine Intensive et Réanimation, CHU Clermont Ferrand, Clermont Ferrand, France. ✉email: cdupuis1@chu-clermontferrand.fr

IL	Interleukin
mHLA-DR	Monocytic human leukocyte antigen-DR
RT-PCR	Reverse transcription polymerase chain reaction
SAPS II	Simplified acute physiology score II
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SFR	French Society of Radiology
SIT	Thoracic Imaging Society
SMD	Skeletal muscle density
SMI	Skeletal muscle index
SOFA	Sepsis-related organ failure assessment
SPILF	Société de Pathologie Infectieuse en Langue Française (French Infectious Diseases Society)
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia

Sarcopenia is a condition characterized by a progressive loss of muscle mass and strength that is particularly prevalent in older individuals and those with comorbidities[1]. It is closely related to frailty and has been identified as an adverse prognostic factor in various diseases, including chronic respiratory failure[2,3] and cancer[4,5], acute conditions such as pneumonia and critical illness[6–8]. Sarcopenia has also been identified as predictors for outcomes in COVID-19 pneumonia[9–12] including ICU admission, need for invasive mechanical ventilation (IMV), and mortality[13–15].

At the end of a prolonged ICU stay, most of the patients can present ICU acquired weakness (ICU-AW)[16], which is associated with longer duration of invasive mechanical ventilation, ICU stay and increased risk of death[17]. Sarcopenia is a major player of the ICU-AW[18] and is closely linked in ICU to preexisting denutrition, calory and protein intakes during ICU stay, but also hypercatabolism and inflammation[19].

COVID-19 patients with acute hypoxic respiratory failure (COVID-AHRF)[20,21], are characterized by a prolonged hypercatabolism[22] and inflammation that can result in the formation of a "cytokine storm" with the secretion of multiple inflammatory mediators, including interleukins. This inflammation can result in COVID-AHRF and increased risk of death[23,24]. In addition, other markers like under-expression of monocytic human leukocyte antigen-DR (mHLA-DR)[25] have revealed patients with severe SARS-CoV 2 pneumonia admitted to the intensive care unit (ICU).

CT-scan has been rapidly recommended for all severe COVID-19 patients to assess respiratory status[11,26]. On those CT-scan, it is possible to obtain a standardized analysis of mysoteatosis using skeletal muscle density (SMD) and the skeletal surface cross-sectional area (CSA) using dedicated software[9]. Even if not recommended at the present time to define sarcopenia, due to lack of universal threshold adapted for all patients, either for surgical patients[27], or the last consensus from the Global Leadership Initiative in Sarcopenia (GLIS)[28], the CSA and SMD measurements obtained at T4 (4th thoracic vertebra) and L3 (3rd lumbar vertebrae) can be used as markers for assessing sarcopenia and myosteatosis. Sarcopenia is related to a decrease of the CSA. Myosteatosis is defined by a reduction in SMD as measured in Hounsfield units (HU)[29]. Those criteria have been used most of the time in oncologic and older patients[30], but also in general cohort of hospitalized patients[31].

Until nowadays, the association between inflammation and muscle loss and their mutual consequences on outcomes have not yet been fully explored for COVID-19 patients admitted in ICU. Furthermore, the correlation between CSA and SMD assessed on T4 and/or L3 have not been also fully explored.

In that context, the aims of our study were to assess among critically ill COVID-19 patients on ICU admission the association between sarcopenia and myosteatosis assessed on CT-scan on L3 and or T4, inflammatory biomarkers and the risk of death at day 90. We also assessed the correlations between the indices of sarcopenia and myosteatosis obtained on CT-scan at the levels L3 and T4.

Materials and methods

Type of study

We conducted a single-centre retrospective observational study, achieved on a database collected prospectively, in the medical ICU of Clermont Ferrand University Hospital, following the TRIPOD guidelines[32]. All patients or their relatives received clear, fair and appropriate information before the consent. Then, all the patients and/or their legal guardian(s) gave their written informed consent for the storage and use for research purposes of the blood samples of the patients collected during routine examinations during the hospital stay. Our study received approval from the ethics committee (Institutional review board (IRB) No. 20.03.20.56342 from the ethic committee called in french: "Comités de protection des personnes (CPP)"-Ile-de-France VI Groupe Hospitalier Pitié-Salpetriêre) in accordance with our local regulations. All the procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Population

We included patients over 18 years of age admitted for severe COVID-19 documented by RT PCR in the medical ICU between July 1, 2020 and November 1, 2021 who had a thoracic CT scan more than 72 h before or after their ICU admission. We excluded patients referred from another ICU, those who decided to limit or stop active therapies in the first two days following ICU admission, and those whose ICU length of stay (LOS) was less than 72 h.

Diagnosis of SARS-CoV-2 infection

The diagnosis of SARS-Co-2 pneumonia was confirmed by a positive PCR test, irrespective of the patient's serological status.

Severe COVID-19 was defined according to WHO criteria by an oxygen saturation < 90% on room air and/or signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute).

Patients with previous immunosuppression on ICU admission gathered patients with organ transplants, acquired immunodeficiency syndrome (AIDS), non-AIDS HIV, corticoids > 1 month or > 2 mg/kg/j, chemotherapy, aplasia, or other immunodepression.

Data collection

All data were prospectively collected including demographics, chronic disease/comorbidities as assessed by the Knaus Scale[33], baseline severity indexes, and simplified acute physiology score (SAPS) II[34], Sequential Organ Failure Assessment (SOFA)[35] scores, treatment and laboratory parameters on admission, including blood count, plasma coagulability markers (D-dimer and fibrinogen levels) and biomarkers of inflammation (CRP, ferritin, IL-1β, IL-6, IL-10, Procalcitonin, mHLA-DR).

Several data were collected throughout ICU stay, including the need for organ assistance including IMV, vasopressor drugs, renal replacement therapy (RRT). The prognostic criteria collected were ICU and hospital LOS, and vital status at ICU discharge and on D90. We consider all-cause mortality at day 90.

Extent of lung parenchymal lesions on CT-scan

Most of the patients underwent thoracic and/or abdominal CT-scan. The percentage of the extent of parenchymal pulmonary lesions was assessed with Thoracic VCAR software (GE Healthcare), a post-processing software that uses an automatic thresholding method based on density measurements in HU. A density threshold greater than − 686 HU (Hounsfield unity) was thus able to quantify areas of condensation or ground glass associated with COVID-19 pneumopathy and differentiate them from healthy lung parenchyma. The software has the advantage of allowing reproducible standardization of the measurement[36].

Measuring Sarcopenia and myosteatosis

We measured muscle surfaces and densities on sections passing through levels L3 and T4 considering all muscles (Figure S1). The measurements were made with SliceOmatic V 5.0 software (Tomovision, Magog, Canada). The HU thresholds for muscle were defined from − 29 to + 150 HU[37], which means that the lower the density of a muscle surface the more it will be considered to be in a state of myosteatosis.

Sarcopenia was defined according to the skeletal muscle index (SMI) (cm^2/m^2). A reduced SMI at level L3 corresponded to a value of < 41 cm^2/m^2 for women and < 43 cm^2/m^2 for men with a body mass index (BMI) < 30 kg/m^2, and < 53 cm^2/m^2 for men with a BMI > 30 kg/m^2[38,39]. At T4 level, a reduced SMI corresponded to a value of < 51.9 cm^2/m^2 for women and < 65.2 cm^2/m^2 for men independently of BMI[40].

Myosteatosis was defined according to SMD. A reduced SMD was defined, at level L3, as < 41 HU for a BMI < 25 kg/m^2 and < 33 HU for a BMI > 25 kg/m^2[38,39]. At level T4, a reduced SMD corresponded to a value of < 36.2 HU for women and < 48 HU for men[40].

Statistical analysis

Patient characteristics were expressed as numbers (percentage) for categorical variables and as median (interquartile range) for continuous variables. Linearity of the continuous covariates was checked carefully. Comparisons were made with Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables, which were dichotomized according to their medians or usual threshold used into the literature if necessary.

The correlations between the variables were explored using Pearson's correlation coefficient and represented by a correlation matrix. The biases between the different indices were investigated with the Bland-Altman plot.

Risk factors for death at D90 were investigated using a Cox survival model. Since we knew the outcomes for all patients at day 90, no competitive risk models were considered. We defined mortality as all-cause mortality. After imputation, uni- and multivariate analyses were performed. Only covariates with less than 15% of missing values were considered into the analyses. Variables with a p-value < 0.1 in univariate analysis were tested for inclusion in the multivariate models. A backward selection of the co-variate was used retaining only variables with a p-value < 0.05 to determine the final multivariate model. The proportionality of the risks was carefully checked. A p-value of less than 0.05 was considered statistically significant. Missing data were imputed linearly. Several sensitivity analyses were performed. First, we conducted complete case analyses, and then we adjusted for all covariates that had a p-value < 0.05 in the univariate analyses. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC) and R (Version 3.4.0; R Core Team, Wien, Austria). The following packages were used for the analyses with R: ggcorrplot; ggplot2, ggsci, gridExtra.

Results

Population

A total of 316 patients were eligible over the inclusion period. The 63 patients who did not have imaging within the defined period and the 16 who were transferred from another ICU were excluded. Finally, 239 patients were included in the study (Figure S2). Their characteristics are presented in Table 1. They had a median age of 68.8 years [60.4; 74.8], a median BMI of 28.8 kg/m^2 [24.6; 32] and were 66.8% male. The main comorbidities were cardiovascular disease (18%) and type 2 diabetes (14%). Overall, 17% of patients were receiving

Median [IQR]/number (%)	All (*N* = 239)	Alive at D90 (*N* = 165)	D90 mortality (*N* = 74)	Pvalue
Number of patients	239	165	74	.
Admission before december 2020	103 (43)	67 (40.6)	36 (48.6)	0.30
Age (yr)	68.8 [60.4 ; 74.8]	66.2 [57.4 ; 72.5]	74.5 [69 ; 79.7]	< 0.01
Sex, men	159 (66.6)	109 (66.1)	50 (67.6)	0.82
Comorbidities*				
BMI > 30 kg/m^2 (body mass index)	106 (44.4)	77 (46.7)	29 (39.2)	0.28
Cardiovascular disease	42 (17.6)	20 (12.1)	22 (29.7)	< 0.01
Respiratory chronic disease	19 (8)	11 (6.7)	8 (10.8)	0.27
Chronic kidney disease	19 (8)	8 (4.8)	11 (14.9)	< 0.01
Chronic liver disease	4 (1.6)	0 (0)	4 (5.4)	< 0.01
Immunosupression§	40 (16.8)	25 (15.2)	15 (20.3)	0.33
Diabetes mellitus	33 (13.8)	19 (11.5)	14 (18.9)	0.13
Time from 1st symptoms to ICU admi (days)	9 [6 ; 12]	10 [8 ; 12]	8 [5 ; 10]	< 0.01
Time from hospital to ICU admi (days)	2 [1 ; 4]	2 [1 ; 4]	2 [1 ; 4]	0.59
Remdesivir	48 (20)	36 (21.8)	12 (16.2)	0.32
Steroids	212 (88.8)	144 (87.3)	68 (91.9)	0.30
Tocilizumab	17 (7.2)	14 (8.5)	3 (4.1)	0.22
SAPS II	35 [29 ; 43]	34 [28 ; 40]	38.5 [34 ; 47]	< 0.01
SOFA	4 [3 ; 6]	4 [3 ; 5]	5 [4 ; 7]	< 0.01
PaO2/FiO2	98 [71 ; 257.2]	105.7 [78.8 ; 290]	76.1 [61.1 ; 147.1]	< 0.01
Extent of lung lesions (%)	45.6 [33.8 ; 59]	44 [31.8 ; 57]	47.8 [35.5 ; 61.9]	0.10
SMI L3 (cm^2/m^2)	43 [36 ; 50.4]	43.9 [36.8 ; 52.1]	40.3 [34.4 ; 47]	0.02
Low SMI L3	159 (66.6)	103 (62.4)	56 (75.7)	0.04
SMI T4 (cm^2/m^2)	61 [50.6 ; 70]	62.4 [51.1 ; 71.8]	56.7 [45 ; 66.9]	< 0.01
Low SMI T4	124 (51.8)	77 (46.7)	47 (63.5)	0.02
SMD L3 (HU)	29 [24 ; 37]	31 [26 ; 39]	26 [22 ; 31]	< 0.01
Low SMD L3	168 (70.2)	105 (63.6)	63 (85.1)	< 0.01
SMD T4 (HU)	39 [33 ; 44]	40 [35 ; 45]	35 [28.4 ; 40]	< 0.01
Low SMD T4	168 (70.2)	106 (64.2)	62 (83.8)	< 0.01
IMV	17 (7.2)	8 (4.8)	9 (12.2)	0.04
Vasopressors	20 (8.4)	7 (4.2)	13 (17.6)	< 0.01
Renal replacement therapy	6 (2.6)	3 (1.8)	3 (4.1)	0.31
Antimicrobial therapy	73 (30.6)	46 (27.9)	27 (36.5)	0.18
Laboratory features on admission				
Neutrophils (G/L) (miss = 33)	6.6 [4.8 ; 9.8]	6.2 [4.8 ; 9.1]	7.3 [4.9 ; 10.7]	0.10
Lymphocytes (G/L) (miss = 33)	0.6 [0.4 ; 1]	0.7 [0.5 ; 1.1]	0.6 [0.4 ; 0.9]	0.28
Procalcitonin (μg/L) (miss = 16)	0.2 [0.2 ; 0.6]	0.2 [0.1 ; 0.5]	0.4 [0.2 ; 1.2]	< 0.01
C-reactive protein (mg/L) (miss = 73)	120 [73 ; 165]	113 [70 ; 161]	130.5 [82 ; 184]	0.19
D-dimers (μg/L) (miss = 4)	1215.6 [773.6 ; 2009.6]	1130 [715 ; 1877]	1494 [1100 ; 2546]	< 0.01
Fibrinogen (g/L) (miss = 10)	7.2 [6.4 ; 8]	7.3 [6.6 ; 8]	7.2 [6 ; 7.9]	0.17
Ferritin (μg/L) (miss = 20)	1060.6 [625.6 ; 1793]	1035 [652.5 ; 1678]	1167.5 [542 ; 1934]	0.55
IL-10 (pg/mL) (miss = 33)	4.4 [2 ; 8.2]	3.5 [1.5 ; 6.6]	6.3 [3.2 ; 11.4]	< 0.01
IL-12(pg/mL) (miss = 34)	0.4 [0 ; 1.6]	0.3 [0 ; 1.8]	0.5 [0 ; 1.5]	0.76
IL-1b (pg/mL) (miss = 34)	0 [0 ; 1]	0 [0 ; 0.8]	0 [0 ; 1.1]	0.36
IL-6 (pg/mL) (miss = 26)	39.2 [14 ; 87.6]	26.2 [10.4 ; 87.6]	47.7 [27.4 ; 87.6]	< 0.01
IL-8 (pg/mL) (miss = 34)	27.8 [16.8 ; 47.8]	22.7 [15.3 ; 36.4]	36.7 [25.6 ; 63.8]	< 0.01
TNFalpha (miss = 34)	0 [0 ; 1.2]	0 [0 ; 1.2]	0 [0 ; 1.3]	0.62
mHLA-DR (Ab/c) (miss = 56)	10,182 [6717 ; 14340]	11,138 [7663.5 ;15821]	7750 [6322 ; 12032]	< 0.01
IL-6/mHLA DR (x 1000) (miss = 63)	4.2 [1.2 ; 8.4]	3 [0.8 ; 7.6]	5.8 [3.5 ; 9.6]	< 0.01
During the whole ICU stay				
Vasopressors	64 (26.8)	16 (9.7)	48 (64.9)	< 0.01
Invasive mechanical ventilation	64 (26.8)	19 (11.5)	45 (60.8)	< 0.01
Renal replacement therapy	34 (14.2)	7 (4.2)	27 (36.5)	< 0.01
Pulmonary embolism	10 (4.2)	5 (3)	5 (6.8)	0.18
Ventilator-associated pneumonia	24 (10)	8 (4.8)	16 (21.6)	< 0.01
Steroids	222 (92.8)	151 (91.5)	71 (95.9)	0.22
Continued				

Median [IQR]/number (%)	All (*N* = 239)	Alive at D90 (*N* = 165)	D90 mortality (*N* = 74)	Pvalue
ICU death	65 (27.2)	0 (0)	65 (87.8)	< 0.01
ICU LOS	6 [4 ; 10]	6 [4 ; 9]	10 [5 ; 16]	< 0.01
Hospital LOS	13 [9 ; 22]	14 [10 ; 24]	13 [8 ; 18]	0.02

Table 1. Description of the cohort and bivariate analysis comparing patients according to whether they were alive or dead at day 90. BMI: Body Mass Index; ICU: Intensive care unit; SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; SMI: Skeletal muscle index; SMD: Skeletal Muscle density; HU: Hounsfield unit); Il: Interleukin; mHLA-DR: monocytic human leukocyte antigen-DR; LOS: length of stay. *According to Knauss scale. §: Organ transplants, AIDS, non-AIDS HIV, corticoids > 1 month or > 2 mg/kg/j, chemotherapy, aplasia, or other immunodepression.

		Univariate			Multivariate*	
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Low SMI L3	1.74	[1.04 ; 2.93]	0.04	1.28	[0.76 ; 2.16]	0.36
Low SMI T4	1.85	[1.16 ; 2.94]	0.01	1.66	[1.03 ; 2.66]	0.04
Low SMD L3	2.77	[1.46 ; 5.23]	< 0.01	1.47	[0.7 ; 3.07]	0.31
Low SMD T4	2.51	[1.37 ; 4.61]	< 0.01	1.55	[0.86 ; 2.79]	0.14

Table 2. Myosteatose and sarcopenia defined by CT-scan and risks of mortality at Day-90: uni-and multivariate analyses. SMI: Skeletal muscle index; SMD: Skeletal Muscle density; L: Lumber; T: Thoracic. *adjustment on age, requirement for vasopressors, procalcitonin, Il6 (See table S1 and S2). Sarcopenia was defined according to the skeletal muscle index (SMI) (cm^2/m^2). A reduced SMI at level L3 corresponded to a value of < 41 cm^2/m^2 for women and < 43 cm^2/m^2 for men with a body mass index (BMI) < 30 kg/m^2, and < 53 cm^2/m^2 for men with a BMI > 30 kg/m^2[238]; Wang et al. (2020). At T4 level, a reduced SMI corresponded to a value of < 51.9 cm^2/m^2 for women and < 65.2 cm^2/m^2 for men independently of BMI[40]. Myosteatosis was defined according to the skeletal muscle density (SMD). A reduced SMD was defined, at level L3, as < 41 HU for a BMI < 25 kg/m^2 and < 33 HU for a BMI > 25 kg/m^2[238]; Wang et al. (2020). At level T4, a reduced SMD corresponded to a value of < 36.2 HU for women and < 48 HU for men[40].

immunomodulatory therapy and 89% corticosteroids. Only 7% of patients on admission were on IMV, 8% on vasopressors and 2.6% on RRT. The average percentage of parenchymal involvement was 45.6% (Table 2).

During ICU stay, 27% of patients required vasopressors, 27% IMV and 14% RRT. The two main complications were VAP, in 10% of cases, and pulmonary embolism, in 4% of patients. Finally, by D90, 72 (30.2%) of the patients had died.

Correlations between patient characteristics at admission are shown in Fig. 1.

Muscle densities at L3 and T4 were highly correlated (r^2=0.79, $p < 0,001$). To a lesser extent, we found a correlation coefficient of 0.64 between the surface area at L3 and T4 ($p < 0,001$). All the correlations between CT-scan markers and inflammatory biomarkers were less than 0.2.

Muscle surface area and density

The median SMI at L3 was 43 [36; 50.4] cm^2/m^2: 159 patients (66.6%) had a reduced SMI at L3, with a significantly higher number in the group who died at D90 (75.7%) than in the group alive at D90 (62.4%, $p = 0.04$). The mean SMI at T4 was 61 [50.6; 70] cm^2/m^2, and a total of 124 patients (51.8%) had a reduced SMI at T4. with a significant difference between the two groups: 46.7% of patients were alive at D90 as against 63.5% who had died ($p = 0.02$).

The mean value of SMD at L3 was 29 HU and a total of 168 patients (70.2%) had reduced SMD at L3 with, once again, a significant difference between the two groups: 63.6% of patients alive at D90 compared with 85.1% deceased ($p < 0.01$).

In T4, the mean SMD was 39 HU, and a total of 168 patients (70.2%) had reduced SMD in T4. There was a significant difference between the two groups: 4.2% of patients alive at D90 compared with 83.8% deceased ($p < 0.01$).

The Bland-Altman difference diagram presented in Fig. 2 shows a mean systematic difference of 18.4 cm^2/m^2 [-4.9;41.6] in SMI between T4 and L3. There was a systematic difference of 7.94 [-3.22;19.1] UH in SMD between T4 and L3.

Risk factors of D90 mortality

The results of the uni- and multivariate analyses are presented in Table S1 and 2. Finally, the factors independently associated with D90 mortality were age, the requirement for vasopressors, procalcitonin and il-6 levels, and reduced muscle surface area in T4 was associated with D90 mortality (HR 1.66 $p = 0.04$). These results are consistent with the sensitivity analyses conducted after imputation (Tables S2 and S3).

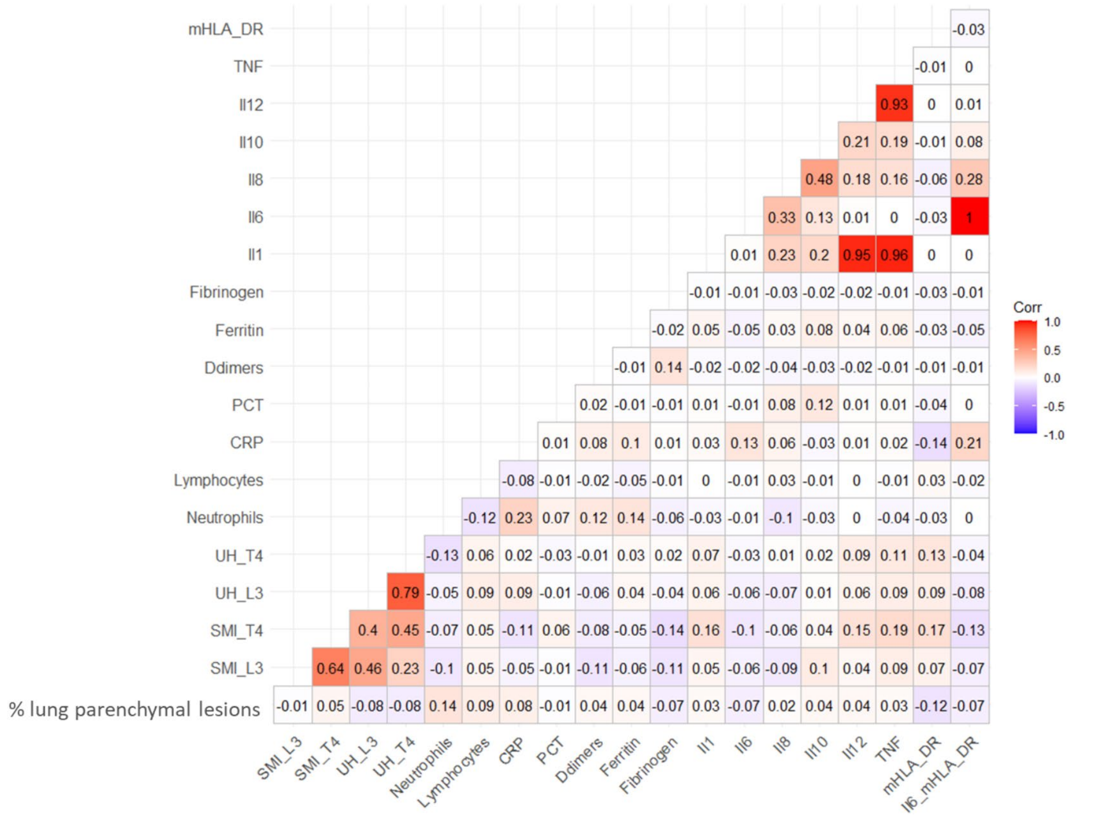

Fig. 1. Correlation between variables on ICU admission. SMI: Skeletal muscle index; SMD: Skeletal Muscle density; Il: Interleukin; mHLA-DR: monocytic human leukocyte antigen-DR; UH: Hounsfield unity; L: Lumbar; T: Thoracic; PCT: Procalcitonin.

Muscle surface area at L3, muscle density at T4 and L3 and the extent of pulmonary lesions were not independently associated with D90 mortality.

Figure 3 shows the areas under the curve (AUC) for the prediction of mortality at D90 as a function of the different laboratory and CT-scan findings of patients on ICU admission.

The best performance was obtained for T4 SMD (0.69, CI [0.61–0.76]).

Discussion

Our study shows that sarcopenia tended to be an independent risk factor for mortality at D90 in patients admitted to ICU care for severe COVID-19. Interestingly, we did not observe a direct correlation between inflammation and sarcopenia. However, incorporating indices of sarcopenia with inflammatory biomarkers improved prognostic accuracy. These findings align with previous research. We also report that assessment of sarcopenia could be achieved at T4 and L3.

In a cohort of ICU patients in the study of Schinas et al.[41], the T10 CSA was significantly associated with survival. The authors also showed a correlation with inflammatory markers. This association could be attributed to increased catabolism during severe COVID-19, driven by elevated inflammation levels[42,43]. Data from intubated patients indicated that higher pectoralis muscle area (PMA) and pectoralis muscle density (PMD) at T4 were linked to shorter ICU stays and successful extubation[43,44] whereas lower muscle density correlated with longer hospitalization and higher in-hospital mortality. This could be partly explained by the fact that sarcopenia impairs the ability to produce adequate respiratory volumes after IMV thus causing a slower recovery of spontaneous breathing[45].

SMI and SMD at T5 and T12 levels had a predictive value for ICU admission and death in COVID-19 patients admitted to the emergency department (ED)[46]. Additionally, thoracic muscle steatosis at the T10 vertebra level was suggested to predict the progression to severe COVID-19[47]. Koehler et al., in COVID-19 patients admitted to the ED, showed also that sarcopenia assessed at T4 and L3 levels was associated with an increased risk of hospitalization in ICU[15]. A meta-analysis conducted by Sumbal et al.[48] shows that the risk of mortality and severity of COVID-19 spikes up to twice in patients with sarcopenia. Thus, chest CT-scans should be analyzed to identify patients at risk of intubation, who should then be kept in a department under continuous monitoring.

Our study specifically highlights the significance of CSA at T4, but not at L3, as a risk factor for mortality. However, reduced CSA and density at both T4 and L3 showed an overall trend towards increased mortality risk. The good correlation between SCA at T4 and L3 levels and of SMD at T4 and L3 levels attests to the reproducibility of this assessment method. This is interesting because most studies assessing sarcopenia are based

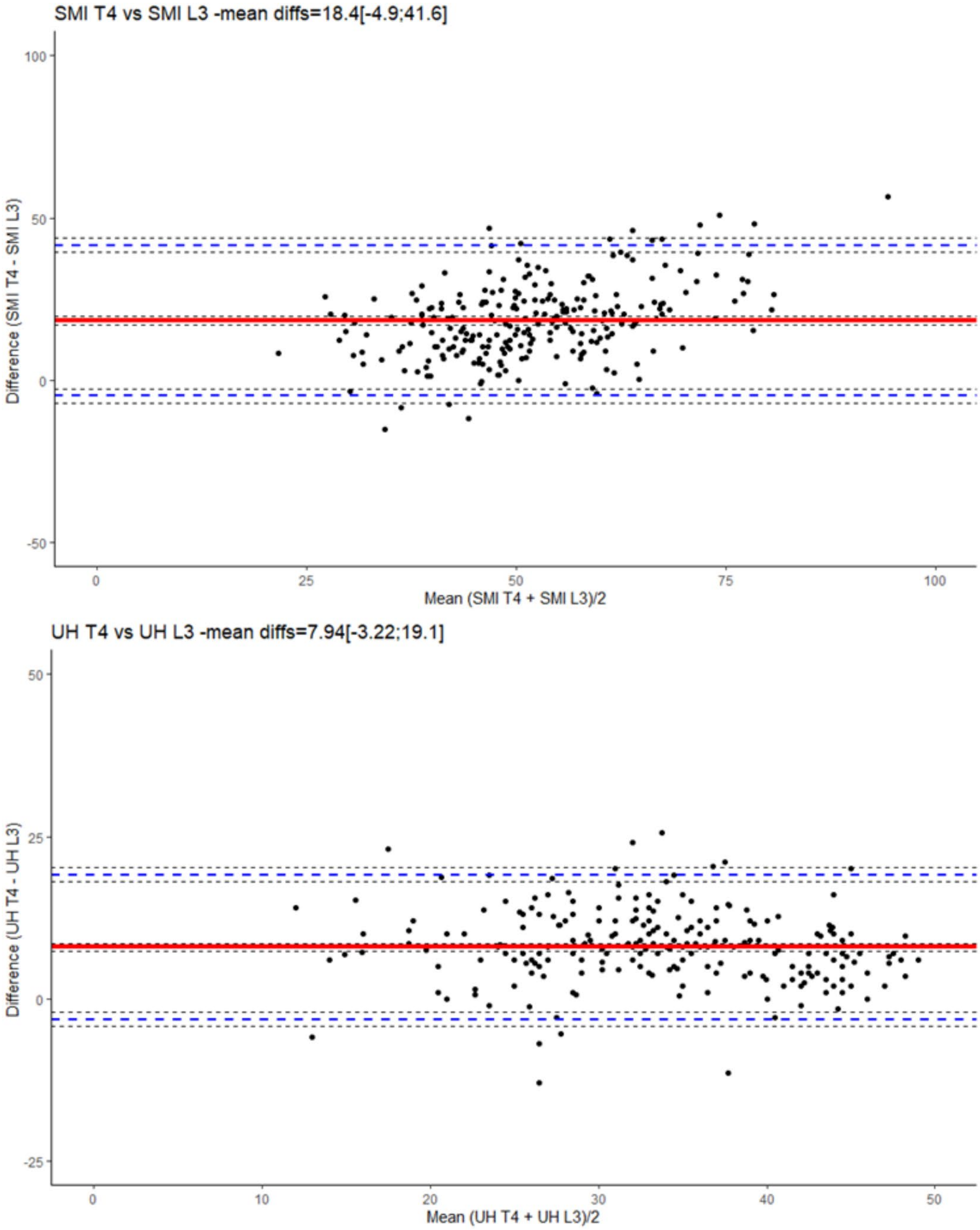

Fig. 2. Bland-Altman difference diagram for muscle density and surface area at L3 and T4. SMI: Skeletal muscle index; SMD: Skeletal Muscle density; UH: Hounsfield unity; L: Lumbar; T: Thoracic.

on CSA and SMD at L3, but this level of slice is not always available, particularly with thoracic CT-scans. Sumbal et al.[49] performed a meta-analysis of 14 articles to assess which vertebral level to use in COVID-19 patients to calculate sarcopenia. Their findings showed that in 31% of cases the thoracic level was most appropriate and in 63% the lumbar vertebral level. They found that sarcopenia calculated at the thoracic vertebral and lumbar levels has different prognostic values, with sarcopenia at the thoracic level showing higher mortality rates than at the lumbar level.

Various other studies have explored associations between body composition using methods other than CT-scan and COVID-19 outcomes which indicated that sarcopenia is linked to an elevated risk of mortality and severity[50]. Looijaard et al.[51] explored the relation between CT-scan and indices obtained by bio-impedance analysis (BIA). CT-derived skeletal muscle area and density were significantly lower in patients with low compared to normal phase angle. One meta-analysis of 62 studies was performed to assess the association between body composition and COVID-19 outcomes. Low phase angle, low muscle echo intensity, and low BIA-estimated muscle mass were associated with increased risk of mortality and ICU admission. Of note, low

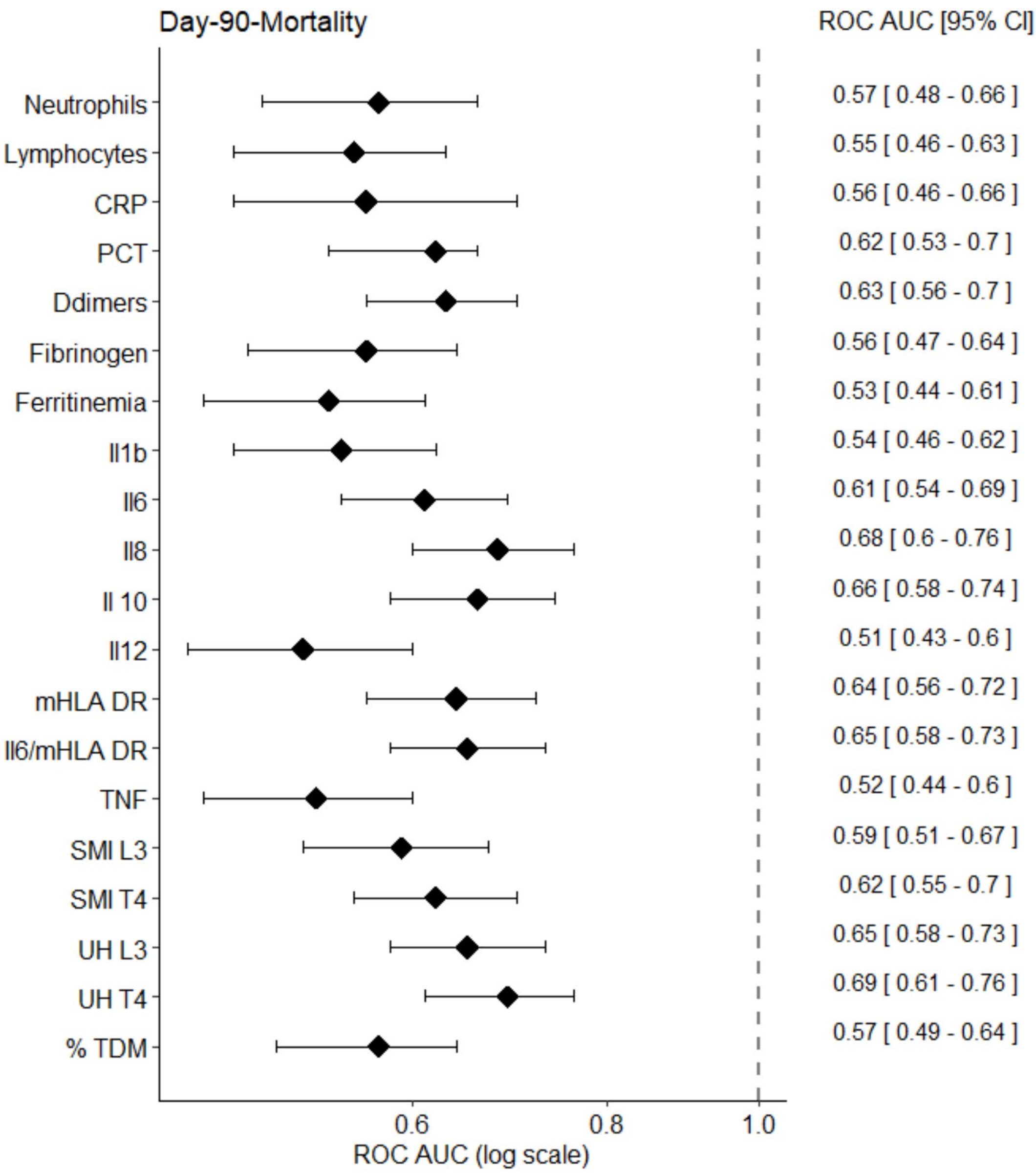

Fig. 3. Prediction of mortality at D90 - ROC curve. SMI: Skeletal muscle index; SMD: Skeletal Muscle density; Il: Interleukin; mHLA-DR: monocytic human leukocyte antigen-DR; UH: Hounsfield unity; L: Lumbar; T: Thoracic; PCT: Procalcitonin.

phase angle has been associated with increased inflammation and oxidative stress, which may affect COVID-19 pathogenesis and severity.

Incorporating biological biomarkers and radiological findings significantly enhanced the prediction of D60 mortality. Notably, high IL-6 levels were associated with an increased risk of mortality, aligning with the concept of a cytokine storm in severe COVID-19 cases.

Prognostication of COVID-19 patients should consider clinical and biological parameters. Systematic assessment of IL-6 levels in patients admitted to intensive care would be useful to plan more active treatment for patients with high levels. After adjustment, we were unable to demonstrate such a correlation with the other specific markers of inflammation, most likely owing to a lack of power in our study. Some studies have also assessed the combined performance of radiological findings and biomarkers to predict COVID-19 outcomes[52]. For instance, the RadScore proposed by Wu et al.[53] was as reliable as their proposed clinical score, and prognostication was improved when clinical and radiological findings were considered together.

Despite these insights, our study has limitations, such as its retrospective nature, limited sample size, and potential selection bias. First, our definition of sarcopenia was solely based on muscle loss without incorporating assessment of muscle function. Second, the cut-off values to define sarcopenia and myosteatosis were derived from oncological cohort that can be not adapted to our cohort. Hence, this may have led to over-classification of patients as sarcopenic yet under representation of the disease burden of comorbidities[39]. Then, we must acknowledge that we didn't know if among included patients, some of them add already sarcopenia, before COVID-19. Furthermore, because of missing data, some covariates could not be tested into the multivariate analyses.

The main strength of the present study is the quality of the data mostly collected prospectively, including inflammatory cytokine and mHLA DR levels. It is one of the first studies focusing on patients with SARS-CoV2 pneumonia admitted to the ICU that has used reliable and reproducible AI software to measure SMD and SCA values at T4 and L3 levels. We also acknowledge that we were able to assess muscle surface area and muscle density at both the L3 and T4 levels, allowing for a comparison between these two regions.

Conclusions

Our findings underscore the independent prognostic value of the muscle area at T4 level in predicting death at D90 in ICU-admitted COVID-19 patients. Although muscle density at T4 and muscle density and area at L3 did not show significance in multivariate analysis, they were almost associated significantly with death at D90 in univariate analysis, highlighting the importance of muscle assessment in managing COVID-19 in the ICU. Combining IL-6 levels with T4 muscle surface area and density analysis could provide valuable insights into the prognosis of COVID-19 patients in intensive care. The correlation between muscle damage assessments at T4 and L3 requires further validation.

Data availability

All the data are available on request at the corresponding author.

Received: 10 June 2024; Accepted: 31 January 2025
Published online: 05 February 2025

References

1. Chianca, V. et al. Sarcopenia: Imaging assessment and clinical application. *Abdom. Radiol.* **47**, 3205–3216. https://doi.org/10.1007/s00261-021-03294-3 (2021).
2. Rozenberg, D. et al. Clinical outcomes associated with computed tomography-based body composition measures in lung transplantation: A systematic review. *Transpl. Int. Off J. Eur. Soc. Organ. Transpl.* **33**, 1610–1625. https://doi.org/10.1111/tri.13749 (2020).
3. Nicholson, J. M. et al. Computed tomography-based body composition measures in COPD and their association with clinical outcomes: A systematic review. *Chron. Respir Dis.* **19**, 14799731221133387. https://doi.org/10.1177/14799731221133387 (2022).
4. Ponholzer, F. et al. Sarcopenia and Mediastinal Adipose Tissue as a prognostic marker for short- and long-term outcomes after primary Surgical treatment for Lung Cancer. *Cancers* **15**, 5666. https://doi.org/10.3390/cancers15235666 (2023).
5. Arayne, A. A., Gartrell, R., Qiao, J., Baird, P. N. & Yeung, J. M. Comparison of CT derived body composition at the thoracic T4 and T12 with lumbar L3 vertebral levels and their utility in patients with rectal cancer. *BMC Cancer*. **23**, 56. https://doi.org/10.1186/s12885-023-10522-0 (2023).
6. Zhang, X-M. et al. Sarcopenia as a predictor of mortality among the critically ill in an intensive care unit: A systematic review and meta-analysis. *BMC Geriatr.* **21**, 339. https://doi.org/10.1186/s12877-021-02276-w (2021).
7. Darden, N. et al. Long-term clinical outcomes in critically ill patients with sepsis and pre-existing low muscle mass: A retrospective cohort study. *BMC Anesthesiol.* **23**, 313. https://doi.org/10.1186/s12871-023-02274-y (2023).
8. Dusseaux, M. M. et al. Skeletal muscle mass and adipose tissue alteration in critically ill patients. *PloS One*. **14**, e0216991. https://doi.org/10.1371/journal.pone.0216991 (2019).
9. Koehler, J. et al. Thoracic sarcopenia as a predictive factor of SARS-COV2 evolution. *Clin. Nutr.* **41**, 2918–2923. https://doi.org/10.1016/j.clnu.2022.01.022 (2022).
10. Yu, Q. et al. Multicenter cohort study demonstrates more consolidation in upper lungs on initial CT increases the risk of adverse clinical outcome in COVID-19 patients. *Theranostics* **10**, 5641–5648. https://doi.org/10.7150/thno.46465 (2020).
11. Recommandations d'imagerie thoracique de la SIT dans le cadre de la Covid-19. (21/09/2020). SFR E-Bull 2020. https://ebulletin.radiologie.fr/actualites-covid-19/recommandations-dimagerie-thoracique-sit-cadre-covid-19-21092020 (accessed February 17, 2023).
12. Li, Y., Yang, Z., Ai, T., Wu, S. & Xia, L. Association of initial CT findings with mortality in older patients with coronavirus disease 2019 (COVID-19). *Eur. Radiol.* **30**, 6186–6193. https://doi.org/10.1007/s00330-020-06969-5 (2020).
13. Ducray, V. et al. Chest CT for rapid triage of patients in multiple emergency departments during COVID-19 epidemic: Experience report from a large French university hospital. *Eur. Radiol.* **31**, 795–803. https://doi.org/10.1007/s00330-020-07154-4 (2021).
14. Burian, E. et al. Intensive care risk estimation in COVID-19 Pneumonia Based on Clinical and Imaging parameters: Experiences from the Munich Cohort. *J. Clin. Med.* **9**, 1514. https://doi.org/10.3390/jcm9051514 (2020).
15. Koehler, J. et al. Thoracic sarcopenia as a predictive factor of SARS-COV2 evolution. *Clin. Nutr. Edinb. Scotl.* **41**, 2918–2923. https://doi.org/10.1016/j.clnu.2022.01.022 (2022).
16. Cederholm, T. et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin. Nutr. Edinb. Scotl.* **38**, 1–9. https://doi.org/10.1016/j.clnu.2018.08.002 (2019).
17. Yang, Z., Wang, X., Wang, F., Peng, Z. & Fan, Y. A systematic review and meta-analysis of risk factors for intensive care unit acquired weakness. *Med. (Baltim).* **101**, e31405. https://doi.org/10.1097/MD.0000000000031405 (2022).
18. Puthucheary, Z. A. et al. Acute skeletal muscle wasting in critical illness. *JAMA* **310**, 1591–1600. https://doi.org/10.1001/jama.2013.278481 (2013).
19. Plank, L. D., Connolly, A. B. & Hill, G. L. Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. *Ann. Surg.* **228**, 146–158. https://doi.org/10.1097/00000658-199808000-00002 (1998).
20. Gujski, M., Jankowski, M., Rabczenko, D., Goryński, P. & Juszczyk, G. The prevalence of Acute Respiratory Distress Syndrome (ARDS) and outcomes in hospitalized patients with COVID-19—A study based on data from the Polish National Hospital Register. *Viruses* **14**, 76. https://doi.org/10.3390/v14010076 (2022).
21. Guan, W. et al. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl. J. Med.* **382**, 1708–1720. https://doi.org/10.1056/NEJMoa2002032 (2020).
22. Dupuis, C. et al. Association of nitrogen balance trajectories with clinical outcomes in critically ill COVID-19 patients: A retrospective cohort study. *Clin. Nutr. Edinb. Scotl.* **41**, 2895–2902. https://doi.org/10.1016/j.clnu.2022.08.023 (2022).
23. Broman, N. et al. IL-6 and other biomarkers as predictors of severity in COVID-19. *Ann. Med.* **53**, 410–412. https://doi.org/10.1080/07853890.2020.1840621 (2021).

24. Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A. & Ng, L. F. P. The trinity of COVID-19: Immunity, inflammation and intervention. *Nat. Rev. Immunol.* **20**, 363–374. https://doi.org/10.1038/s41577-020-0311-8 (2020).
25. Spinetti, T. et al. Reduced Monocytic Human Leukocyte Antigen-DR expression indicates immunosuppression in critically ill COVID-19 patients. *Anesth. Analg.* **131**, 993–999. https://doi.org/10.1213/ANE.0000000000005044 (2020).
26. SRLF, S. F. A. R. & Recommandations-dexperts accessed August 26, -COVID-19-10-Mars-2020.pdf 2020. (2024). https://www.srlf.org/wp-content/uploads/2020/03/Recommandations-dexperts-COVID-19-10-Mars-2020.pdf
27. Koh, F. H. et al. Perioperative management of Sarcopenia in patients undergoing major surgeries in Singapore: A modified Delphi consensus. *Int. J. Surg. Lond. Engl.* **110**, 4552–4558. https://doi.org/10.1097/JS9.0000000000001515 (2024).
28. Kirk, B. et al. The conceptual definition of Sarcopenia: Delphi Consensus from the Global Leadership Initiative in Sarcopenia (GLIS). *Age Ageing*. **53**, afae052. https://doi.org/10.1093/ageing/afae052 (2024).
29. Goodpaster, B. H. et al. The loss of skeletal muscle strength, Mass, and quality in older adults: The Health, Aging and Body Composition Study. *J. Gerontol. Biol. Sci. Med. Sci.* **61**, 1059–1064. https://doi.org/10.1093/gerona/61.10.1059 (2006).
30. Ackermans, L. L. G. C. et al. Screening, diagnosis and monitoring of Sarcopenia: When to use which tool? *Clin. Nutr. ESPEN*. **48**, 36–44. https://doi.org/10.1016/j.clnesp.2022.01.027 (2022).
31. Baumgartner, A. et al. Association of CT-based diagnosis of Sarcopenia with prognosis and treatment response in patients at risk of malnutrition - A secondary analysis of the Effect of early nutritional support on Frailty, Functional outcomes, and recovery of malnourished medical inpatients trial (EFFORT) trial. *Clin. Nutr. Edinb. Scotl.* **42**, 199–207. https://doi.org/10.1016/j.clnu.2022.12.006 (2023).
32. Collins, G. S., Reitsma, J. B., Altman, D. G., Moons, K. G. M. & members of the TRIPOD group. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. *Eur. Urol.* **67**, 1142–1151. https://doi.org/10.1016/j.eururo.2014.11.025 (2015).
33. Knaus, W. A. et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* **100**, 1619–1636 (1991).
34. Le Gall, J. R., Lemeshow, S. & Saulnier, F. A new simplified Acute Physiology score (SAPS II) based on a European/North American multicenter study. *JAMA* **270**, 2957–2963 (1993).
35. Vincent, J. L. et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Crit. Care Med.* **26**, 1793–1800 (1998).
36. Mader, C. et al. Quantification of COVID-19 opacities on chest CT – evaluation of a fully automatic AI-approach to noninvasively differentiate critical Versus Noncritical patients. *Acad. Radiol.* **28**, 1048–1057. https://doi.org/10.1016/j.acra.2021.03.001 (2021).
37. Aubrey, J. et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol.* **210**, 489–497. https://doi.org/10.1111/apha.12224 (2014).
38. Martin, L. et al. Cancer Cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, Independent of Body Mass Index. *J. Clin. Oncol.* **31**, 1539–1547. https://doi.org/10.1200/JCO.2012.45.2722 (2013).
39. Wang, S. et al. The value of L3 skeletal muscle index in evaluating preoperative nutritional risk and long-term prognosis in colorectal cancer patients. *Sci. Rep.* **10**, 8153. https://doi.org/10.1038/s41598-020-65091-0 (2020).
40. van der Kroft, G. et al. Low thoracic muscle radiation attenuation is associated with postoperative pneumonia following partial hepatectomy for colorectal metastasis. *HPB* **22**, 1011–1019. https://doi.org/10.1016/j.hpb.2019.10.1532 (2020).
41. Schinas, G. et al. Radiologic features of T10 paravertebral muscle Sarcopenia: Prognostic factors in COVID-19. *J. Clin. Med. Res.* **15**, 368–376. https://doi.org/10.14740/jocmr4963 (2023).
42. Lang, T. et al. Sarcopenia: Etiology, clinical consequences, intervention, and assessment. *Osteoporos. Int. J. Establ Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA*. **21**, 543–559. https://doi.org/10.1007/s00198-009-1059-y (2010).
43. Antonarelli, M. & Fogante, M. Chest CT-Derived muscle analysis in COVID-19 patients. *Tomogr Ann. Arbor Mich.* **8**, 414–422. https://doi.org/10.3390/tomography8010034 (2022).
44. Damanti, S. et al. Influence of reduced muscle mass and quality on ventilator weaning and complications during intensive care unit stay in COVID-19 patients. *Clin. Nutr. Edinb. Scotl.* **41**, 2965–2972. https://doi.org/10.1016/j.clnu.2021.08.004 (2022).
45. Ali, A. M. & Kunugi, H. Screening for Sarcopenia (Physical Frailty) in the COVID-19 era. *Int. J. Endocrinol.* **2021**, 5563960. https://doi.org/10.1155/2021/5563960 (2021).
46. Schiaffino, S. et al. CT-derived chest muscle Metrics for Outcome Prediction in patients with COVID-19. *Radiology* **300**, E328–E336. https://doi.org/10.1148/radiol.2021204141 (2021).
47. Yi, X. et al. Myosteatosis predicting risk of transition to severe COVID-19 infection. *Clin. Nutr. Edinb. Scotl.* **41**, 3007–3015. https://doi.org/10.1016/j.clnu.2021.05.031 (2022).
48. Siahaan, Y. M. T., Hartoyo, V., Hariyanto, T. I. & Kurniawan, A. Coronavirus disease 2019 (Covid-19) outcomes in patients with Sarcopenia: A meta-analysis and meta-regression. *Clin. Nutr. ESPEN*. **48**, 158–166. https://doi.org/10.1016/j.clnesp.2022.01.016 (2022).
49. Sumbal, R., Sumbal, A. & Ali Baig, M. M. Which vertebral level should be used to calculate Sarcopenia in covid-19 patients? A systematic review and meta-analysis. *Clin. Nutr. ESPEN*. **56**, 1–8. https://doi.org/10.1016/j.clnesp.2023.04.022 (2023).
50. Hocaoglu, E., Ors, S., Yildiz, O. & Inci, E. Correlation of Pectoralis muscle volume and density with severity of COVID-19 pneumonia in adults. *Acad. Radiol.* **28**, 166–172. https://doi.org/10.1016/j.acra.2020.11.017 (2021).
51. Looijaard, W. G. P. M. et al. Identifying critically ill patients with low muscle mass: Agreement between bioelectrical impedance analysis and computed tomography. *Clin. Nutr. Edinb. Scotl.* **39**, 1809–1817. https://doi.org/10.1016/j.clnu.2019.07.020 (2020).
52. Zhang, K. et al. Clinically Applicable AI system for Accurate diagnosis, quantitative measurements, and prognosis of COVID-19 Pneumonia using computed tomography. *Cell* **181**, 1423–1433e11. https://doi.org/10.1016/j.cell.2020.04.045 (2020).
53. Wu, Q. et al. Radiomics analysis of computed tomography helps predict poor prognostic outcome in COVID-19. *Theranostics* **10**, 7231–7244. https://doi.org/10.7150/thno.46428 (2020).

Acknowledgements
We thank Jeffrey Watts for help in preparing the manuscript. We thank the Michelin Corporate Foundation for the grant.

Author contributions
"Conceptualization, RCdB, BS, CD, LC; methodology, BS, CD.; software, CD.; validation, BS., CD, LC, RCdB; formal analysis, CD; investigation, RCdB, BS, CD; resources, BS.; data curation, CD, RCdB, BB, BE, YB, LC, BS, CD writing—original draft preparation, RCdB, CD.; LC writing—review and editing, BB, BE, YB, BS visualization, CD, RCdB; supervision, LC, CD.; project administration, BS; funding acquisition, BS. All authors have read and agreed to the published version of the manuscript."

Funding
This study was supported by a grant from the Michelin Corporate Foundation. The funders had no role in study

design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests
The authors declare no competing interests.

Consent for publication
All patients or their relatives received clear, fair and appropriate information and gave their written consent for the storage and use for research purposes of the blood samples of the patients collected during routine examinations during the hospital stay (IRB No. 20.03.20.56342 from the CPP-Ile-de-France VI Groupe Hospitalier Pitié-Salpetriêre).

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-88914-4.

Correspondence and requests for materials should be addressed to C.D.

Reprints and permissions information is available at www.nature.com/reprints.