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## Clinical Nutrition

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Original article

# Association of bioelectric impedance analysis body composition and disease severity in COVID-19 hospital ward and ICU patients: The BIAC-19 study

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## ARTICLE INFO

## Article history:

Received 5 August 2020

Accepted 14 October 2020

## Keywords:

COVID-19

SARS-CoV-2

Body composition

Fat mass

Fat-free mass

Lean body mass

## SUMMARY

**Background:** The current severe acute respiratory syndrome coronavirus 2 pandemic is unprecedented in its impact. It is essential to shed light on patient characteristics that predispose to a more severe disease course. Obesity, defined as a BMI > 30 kg/m<sup>2</sup>, is suggested to be one of these characteristics. However, BMI does not differentiate between fat mass and lean body mass, or the distribution of fat tissue. The aim of the present study was to assess the body composition of COVID-19 patients admitted to the ward or the ICU and identify any associations with severity of disease.

**Methods:** We performed an observational cross-sectional cohort study. Bioelectric impedance analysis was conducted amongst all confirmed COVID-19 patients admitted to the ward or ICU of our hospital in the Netherlands, between April 10 and 17, 2020. Body water measurements and derived values were recalculated to dry weight, using a standard ratio of extracellular water to total body water of 0.38. Data were compared between the ward and ICU patients, and regression models were used to assess the associations between baseline characteristics, body composition, and several indicators of disease severity, including a composite score composed of mortality, morbidity, and ICU admission.

**Results:** Fifty-four patients were included, of which 30 in the ward and 24 in the ICU. The mean age was 67 years (95%-CI 64–71), and 34 (63%) were male. Mean BMI was 29.7 (95%-CI 28.2–31.1) kg/m<sup>2</sup> and did not differ between groups. Body composition values were not independently associated with disease severity. In multiple logistic regression analyses, a low phase angle was associated with COVID-19 severity in the composite score (OR 0.299, p = 0.046).

**Conclusion:** We found no significant associations between body composition, including fat mass, visceral fat area, and fat-free mass, and disease severity in our population of generally overweight COVID-19 patients. A lower phase angle did increase the odds of severe COVID-19. We believe that factors other than body composition play a more critical role in the development of severe COVID-19.

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## 1. Introduction

Severe acute respiratory syndrome coronavirus-2, SARS-CoV-2, has rapidly spread across countries and continents since its first

appearance in late 2019, causing high incidences of Corona Virus Disease-2019 (COVID-19). Rates of intensive care (ICU) admission are 10.9% among hospitalized COVID-19 patients [1]. ICU patients with severe COVID-19 typically receive prolonged invasive mechanical ventilation with a reported median of 18 days and a case-fatality rate up to 49% [2,3]. Studies describing characteristics of COVID-19 patients requiring hospitalization or ICU admission show these factors correlate with advanced age, male sex, high body mass index (BMI), and several obesity-related comorbidities [4–7]. Among COVID-19 ICU patients, obesity is frequently encountered.

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<https://doi.org/10.1016/j.clnu.2020.10.023>

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**List of abbreviations**

ARDS	acute respiratory distress syndrome
BIA	bioelectric impedance analysis
BMI	body mass index
CFB	cumulative fluid balance
CI	confidence interval
CK	creatinine kinase
COVID-19	Corona Virus Disease-2019
CRP	C-reactive protein
ECW	extracellular water
FFM	Fat free mass
HLOS	hospital length of stay
ICU	intensive care unit
ICW	intracellular water

IQR	interquartile range
LOS	length of stay
LTP	limited treatment plan
PA	(50 kHz total body) phase angle
PBF	percentage body fat
RT-PCR	real-time reverse transcriptase-polymerase chain reaction assay
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SLM	soft lean mass
SMI	skeletal muscle mass index
SMM	skeletal muscle mass
SOFA	sequential organ failure assessment
TBW	total body water
VFA	visceral fat area

Increased disease severity with increasing BMI has been shown [8]. High BMI is a risk factor for hospitalization in persons <60 years of age, a group otherwise less severely affected [9]. Parallels can be drawn with other viral infections, such as H1N1 influenza, that disproportionately impact obese individuals [6,10,11].

A hypothesis is that obese individuals have decreased respiratory volumes and lung compliance due to abdominal obesity [6,10,11]. However, adipose tissue may also serve as a reservoir for SARS-CoV-2, predisposing obese individuals to a higher or more persistent viral load [12–15]. As men are more often and more severely affected by COVID-19 compared with women, despite a lower incidence of obesity, it could be hypothesized that not merely fat percentage, but the location of fat tissue is essential, as men are more prone to visceral fat accumulation [16]. A possible parallel is found in hepatitis C, where visceral obesity is associated with a higher viral load [17].

Addressing which factors influence susceptibility to a severe course of COVID-19 is essential to aid in prevention, earlier treatment, and organization of health care. As such, BMI as a distinguishing factor is inadequate, as it does not differentiate between different tissues, nor the fat tissue distribution. Several studies have demonstrated that high BMI was associated with lower mortality in critically ill, pneumonia, and Acute Respiratory Distress Syndrome (ARDS) patients [18–21]. These findings could be explained by the lack of discriminatory power of BMI to differentiate between body fat and lean mass and the higher absolute amount of lean mass in non-sarcopenic obesity, compared with individuals with an ideal-weight BMI [22]. Indeed, in critically ill patients, it has been shown that BMI is not an independent predictor of mortality when corrected for muscle area [23].

Bioelectrical impedance analysis (BIA) is a validated, non-invasive method for assessing body composition. It measures the opposition to an alternating current passing through body compartments (resistance) and the delay in conduction by membranes (reactance). BIA uses these measurements to estimate the contribution of various tissues to the (segmental) body weight accurately and provides markers for cellular integrity (phase angle). BIA is not yet widely implemented in the ICU, partly because the interpretation of some results is complicated in case of altered hydration status, as is common amongst the critically ill [24]. However, methods to calculate dry body weight values have been described for dialysis patients, where fluid overload is prevalent [25,26]. The ratio between extracellular and total body water, as an indicator of hydration status, is easy to use, intuitive and validated as a predictor of survival in these patients [27,28]. This provides a theoretical justification to apply this technique to ICU patients.

In this study, we aimed to measure BIA body composition amongst COVID-19 patients in the ward and the ICU to uncover associations between body composition and the course of the disease.

## 2. Methods

### 2.1. Study setting

This cross-sectional observational cohort study was performed at Gelderse Vallei Hospital, a University-affiliated teaching hospital in Ede, The Netherlands. The hospital has two ICU units, with 12 and 5 beds, respectively. During the COVID-19 pandemic two additional ICU units were opened in the operating theatre, adding to a total of 29 ICU beds. Between April 10 and 17, 55 SARS-CoV-2 patients were admitted in our hospital. Nationally, on April 13th 2020, a total of 26,551 people had tested positive for SARS-CoV-2, of whom 8729 had been hospitalized, and 2351 had been admitted to ICU [29, 30]. Up until that day a cumulative total of 2823 SARS-CoV-2 positive people had died, of whom 494 in ICU [30]. At the time of the study, the hospital did not participate in any COVID-19 related clinical trials.

### 2.2. Study design and participants

All adult patients (aged  $\geq 18$  years) with SARS-CoV-2 infection, confirmed by real-time reverse transcriptase-polymerase chain reaction assay (RT-PCR) of nasal and pharyngeal swabs, or strong clinical suspicion of COVID-19 in addition to radiological CORADS classification score  $\geq 3$ , in spite of negative initial RT-PCR (conform standard practice in the Netherlands at that time), were eligible for inclusion. Exclusion criteria were pregnancy, presence of electrical implants such as pacemakers or implantable cardioverter defibrillators, wounds or skin damage at the designated electrode sites, or inability to maintain posture during the measurement (i.e., 5 min). The institution's ethics board approved this study. Written informed consent was obtained from all patients or their legal representatives. The study was registered in the Netherlands Trial Register (number NL8562).

### 2.3. BIA measurements

BIA measurements were conducted by a trained researcher between April 10–17th 2020. Body composition measurements were performed with the InBody S10® (InBody Co., Ltd., Seoul, Korea). This multi-frequency, segmental impedance analyzer requires height, weight, and sex as input parameters. The number of days from hospital admission to BIA measurement was recorded.

The most recent measured weight was used. In the ICU, all patients are weighed daily on a bed with incorporated weighing scale. Ward patients are weighed upon admission and from thereon daily when feasible. For BIA measurements, the most recent weight was used. Height as recorded upon hospital admission was used. Measurements were performed in a seated or supine position with reusable electrodes attached to the left and right thumb and index finger and both ankles. The measurements typically took 3–5 min.

The InBody S10 uses segmental impedance and reactance at multiple frequencies to determine total body water (TBW), (segmental) extracellular water (ECW), and the individual ECW/TBW-ratio (Fig. 1). High-frequency currents pass through the TBW, whereas low-frequency currents cannot penetrate cell membranes and flow exclusively through the ECW. Henceforth, it uses validated methods to estimate fat-free mass (FFM), (segmental) soft lean mass (SLM), mineral mass, bone mineral content (BMC), percentage body fat (PBF), visceral fat area (VFA), (segmental) skeletal muscle mass (SMM) and protein mass, in addition to several ratios. Furthermore, individual reference ranges based on sex, age, length, and weight for some values, based on ideal body composition, are provided. In addition, a 50 kHz phase angle (PA) is deduced. PA shows the relationship between reactance and resistance and is regarded a biological marker of cellular health. In health, high cell mass volume and robust cell membranes cause delayed signals and thereby a higher phase angle, whereas ICU patients tend to have a low phase angle ( $\leq 5^\circ$ ).

To correct for iatrogenic over- or dehydration of the extracellular compartment, leading to over- or underestimation of derived values, estimated values derived from ECW were recalculated to dry, or euhydrated weight, using a standardized ECW/TBW of 0.38 (reference value for healthy persons).

#### 2.4. Data collection

Demographic, radiological and clinical data were collected from local electronic medical record systems MetaVision® (iMDsoft, Tel Aviv, Israel) and NeoZIS® (MI Consultancy, Katwijk, The Netherlands). The recorded data included: age, sex, co-morbidities, clinical scores, laboratory results, radiological scores, limited treatment plans (LTP), and body temperature. Cumulative fluid balance (CFB) on the BIA measurement day was recorded whenever

available in ICU patients. CFB is not recorded routinely in ward patients in our hospital.

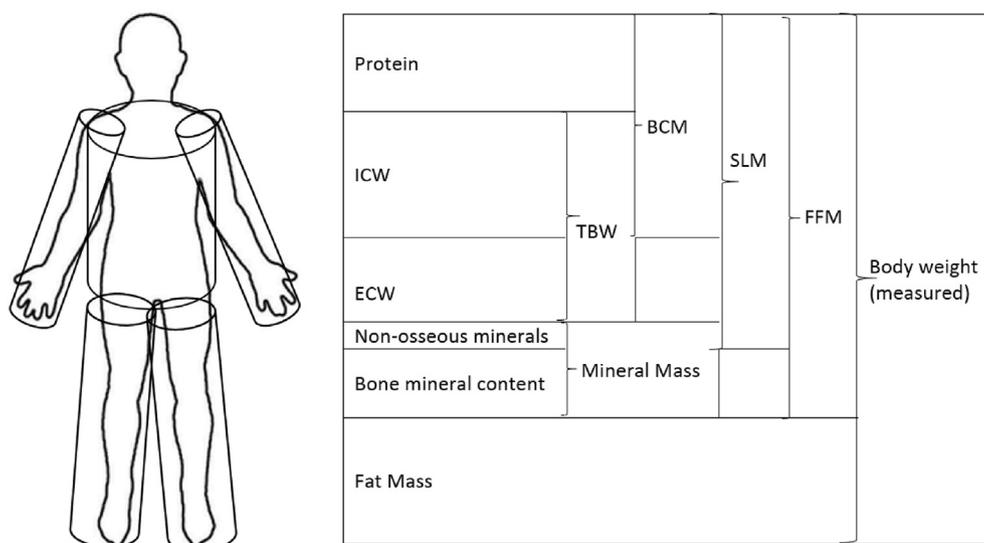
The 28-day outcomes, including ICU- and hospital free days, complications, organ support free days (e.g., ventilation-free days and vasopressor-free days), and mortality were recorded. Expected complications were thrombo-embolic events, renal failure and delirium. Other complications were considered when occurring twice or more in the study population. Furthermore, total ICU and hospital length of stay (ICU LOS resp. HLOS), and hospital discharge destination were recorded.

Disease severity was defined in multiple ways. First, ICU admission for severe COVID-19 was considered. Additional parameters were 28-day mortality and complications. A composite score of ICU-admission and complications, including mortality, was created. A score of 1 indicated that at least one of the criteria was met, while a score of 0 was assigned to those patients without ICU admission and complications. For the ICU patient group, ventilation-free days and vasopressor-free days, were considered continuous outcome measures related to disease severity.

#### 2.5. Statistical analysis

Continuous values are reported as mean (95%-CI) for normally distributed data or median [IQR] for non-normally distributed data. Discrete data are presented as numbers (%). Differences between ICU and ward groups were assessed using independent samples t-tests for continuous data or Chi-squared tests for categorical data. When test assumptions were not met, Mann–Whitney U tests or Fisher's exact tests are used. A sensitivity analysis was performed with the same tests, excluding patients with LTP, waiving ICU admission.

Simple regression analysis was performed for associations between baseline characteristics and disease severity, and for BIA values and disease severity. For binary outcomes, binary-logistic regression was used. Continuous outcomes were univariately analyzed by Poisson regression. When assumptions for Poisson regression were not met, negative binomial regression was used. Multiple logistic regression analysis was performed for BIA values with a p-value  $\leq 0.10$  in simple regression analysis. Continuous outcomes were univariately analyzed by Poisson regression. Other



**Fig. 1.** Body composition principles whereupon bioelectric impedance analysis derived estimations are based. Abbreviations: ICW, intracellular water; TBW, total body water; ECW, extra-cellular water; BCM, body cell mass; SLM, soft lean mass; FFM, fat-free mass; SMM, skeletal muscle mass; SMI, skeletal muscle mass index.

covariates were age, sex, SOFA-score and time between admission and measurement.

IBM SPSS statistics 26 (IBM Corp, Armonk, NY, USA) was used for all analyses. Only two-sided analyses were used. P-values <0.05 were considered statistically significant.

### 3. Results

Between April 10 and April 17, 2020, 55 patients were eligible for inclusion (Fig. 2). One patient declined participation; none were excluded. Four (ward) patients (7%) were confirmed by strong clinical suspicion and CORADS  $\geq 3$  despite negative initial RT-PCR (not repeated), all others had a positive initial RT-PCR. Two patients were briefly (<24 h) admitted to the ICU and did not receive any specialized care before discharge; therefore, they were analyzed in the ward-group. In total, 54 patients (mean age 67 (95%-CI 64–71); 34 males (63%), admitted to the ward (n = 30) or ICU (n = 24) underwent BIA measurements. All the included patients were white of Western European descent. The mean BMI of all patients was 29.7 (95% CI 28.2–31.1), with no significant difference between ward and ICU patients (Table 1). Upon hospital admission ICU patients compared with ward patients had higher SOFA scores (6[IQR 5–7] vs. 2[IQR 2–3];  $p < 0.001$ ) and serum creatine kinase (CK) (n = 47; 174[IQR 117–423] vs. 97[IQR 45–139],  $p = 0.002$ ). No other significant differences between groups in baseline characteristics were found.

Dry weight body composition of all patients is shown in Table 2. No logistical or physical barriers were encountered in performing BIA measurements. Time from ICU admission to measurement was

10[IQR 3–15] days. Median SOFA score on the measurement day was significantly higher in ICU patients than in ward patients (3 [IQR 1–5] resp. 1[IQR 1–2],  $p = 0.009$ ). ICU patients had a mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 218 (95% CI 177–260) on their measurement day, eight (33%) were on vasopressors. The median CFB was 3.95 [IQR 1.60–6.47] liters on the day of measurement, as recorded in 19 ICU patients.

Body composition of ward and ICU patients did not differ significantly concerning dry TBW, fat mass, percentage body fat, and VFA. ICU patients had significantly higher FFM, SLM, SMI, and water measures, including fluid overload, ECW-ratio (ECW/TBW). The phase angle was significantly lower in the ICU group. Table 2 [31–33].

The 28-day outcome measures are summarized in Table 3 and largely favor ward patients. Thirteen of the 30 ward patients (43.3%) had LTPs. A sensitivity analysis excluding LTP patients did not yield any different findings (eTables 1–3). All patients who died in the ward (5(16.7%)) had LTPs preventing ICU admission.

ICU patients had a median of 21[IQR 16–23] vasopressor-free days, and 13[IQR 8–17] invasive ventilation-free days, 12 patients (50%) were ventilated in the prone position. Ten (41.6%) ICU patients received insulin therapy, and one patient (4.2%) required renal replacement therapy. The HLOS for ward patients was 8(95%-CI 5–12), and 26(95%-CI 20–38) days for ICU patients ( $p < 0.01$ ). For ICU patients, the ICU LOS was 18(95%-CI 12–32) days.

#### 3.1. Predictive modeling

Thirty-four patients met the criteria of the composite outcome score, while 20 were not admitted to the ICU and had no complications. Simple regression analysis for BIA values showed several associations (eTable 4). Table 4 summarizes the odds ratios derived from the multiple regression analysis, with age, sex, SOFA score at admission and days between hospital admission and measurement used as covariates.

None of the BIA values, including fat mass, VFA, and FFM, was significantly associated with being admitted to the ICU. More fluid overload, higher ECW/TBW-ratio, and decreased PA were associated with increased risk for mortality. The composite outcome score yielded a significant inverse association with PA (OR 0.299,  $p = 0.046$ ).

### 4. Discussion

We measured body composition by BIA in COVID-19 patients admitted to general wards and the ICU. Although the average patient was overweight, we did not find differences in BMI, nor significant associations between fat mass, fat distribution (visceral fat localization), or fat-free mass (representing the lean body mass) and the severity of disease. However, a lower phase angle at 50 kHz was associated with an increase in disease severity, reflected by the need for ICU admission, morbidity and mortality.

Multiple studies have shown an association between increased BMI and hospital and ICU admission, mechanical ventilation, and mortality in COVID-19 patients [2,8,34–36]. Obesity-related comorbidities are prevalent amongst individuals infected by COVID-19<sup>5, 7</sup>. In 2016, the World Health Organization estimated that 39% of all adults worldwide were overweight (BMI>25 kg/m<sup>2</sup>), and 13% were classified as obese (BMI>30 kg/m<sup>2</sup>) [37]. However, BMI does not incorporate the quantity and distribution of different tissues and is a crude estimation of body composition. Previously, this has led to misinterpretations due to ethnic variability in body ratios, proportion of subcutaneous versus visceral fat, and contribution of muscle mass to body weight [38]. The latter is likely the explanation behind the obesity-mortality-paradox, as it suggested obesity is

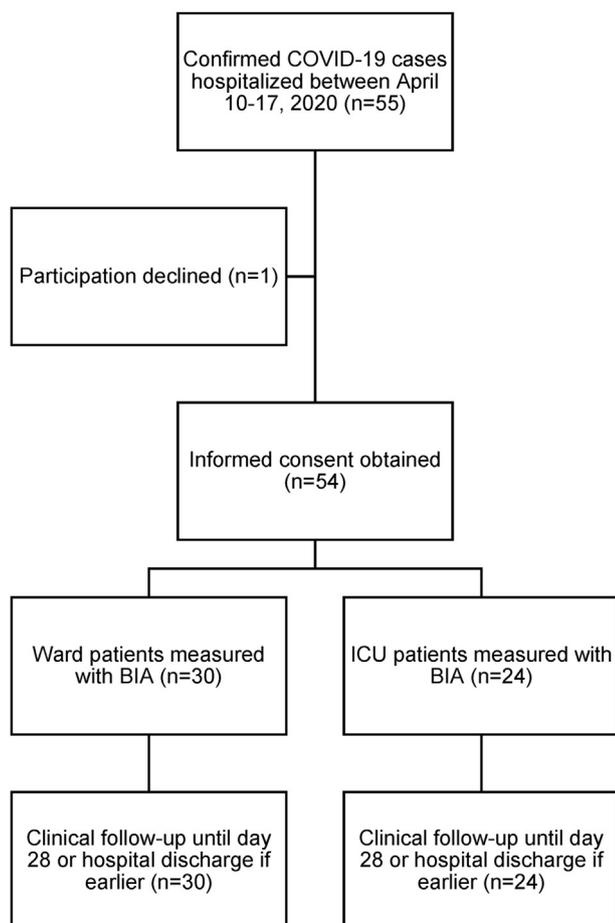


Fig. 2. Study flow diagram.

**Table 1**  
Patient characteristics upon hospital admission<sup>a</sup>.

	All Patients (n = 54) <sup>b</sup>	Ward patients (n = 30)	ICU patients (n = 24)	p- value
Age, mean (95%-CI), years	67 (64–71)	69 (64–74)	66 (61–70)	0.268
Males, no.(%)	34 (63%)	17 (57%)	17 (71%)	0.284
<b>Co- morbidities</b>				
Diabetes, no.(%)	14 (25.9%)	8 (26.7%)	6 (25.0%)	0.890
Hypertension, no.(%)	18 (33.3%)	13 (43.3%)	5 (20.8%)	0.081
Chronic lung disease, no.(%)	14 (25.9%)	9 (30.0%)	5 (20.8%)	0.445
Coronary artery disease, no.(%)	5 (9.3%)	3 (10.0%)	2 (8.3%)	1.000
<b>Clinical scores</b>				
Barthel index	20 [19–20]	20 [18–20]	20 [20–20]	0.171
Frailty score	2 [1–3]	3 [1–5]	2 [1–3]	0.305
APACHE II score	12 [9–15]	11.5 [9–16]	13 [10–14]	0.530
SOFA score	4 [2–6]	2 [2–3]	6 [5–7]	<b>&lt;0.001</b>
<b>Laboratory results</b>				
Hemoglobin, mmol/L (n = 53)	8.8 [7.7–9.6]	8.8 [7.7–9.6]	8.4 [7.7–9.6]	0.929
Leukocytes, 10 <sup>9</sup> /L (n = 53)	8.8 [6.3–11.0]	8.4 [6.3–10.7]	9.2 [6.2–11.8]	0.775
Thrombocytes, 10 <sup>9</sup> /L (n = 53)	230 [183–314]	226 [193–283]	261 [166–320]	0.520
Ferritin, µg/L (n = 12)	1300 [812–2208]	1021 [397–1998]	1470 [894–2410]	0.308
Triglycerides, mmol/L (n = 5)	1.7 [1.1–2.3]	0.8 (–)	1.8 [1.4–2.4]	0.157
C-reactive protein, mg/L	126 [72–212]	106 [72–192]	164 [67–235]	0.413
Serum creatinin, µmol/L (n = 52)	81 [67–116]	81.5 [66–111]	80.5 [68–126]	0.811
Ureum, mmol/L (n = 53)	6.9 [5.4–10.7]	6 [5.5–12.1]	7.3 [5.0–9.8]	0.886
Creatinine Kinase, U/L (n = 47)	117 [59–292]	97 [45–139]	174 [117–423]	<b>0.002</b>
D-dimer, mcg/ml (n = 9)	3.27 [1.98–9.54]	9.67 (–)	2.56 [1.48–2.56]	0.079

Abbreviations: ICU, Intensive Care Unit; CI, confidence interval; APACHE II, Acute Physiology And Chronic Health Evaluation II; SOFA, sequential organ failure assessment. Subheadings and significant results  $p < 0.05$  are in bold.

<sup>a</sup> Data are presented as median and interquartile range unless otherwise reported.

<sup>b</sup> Unless otherwise reported, due to missing data.

**Table 2**  
Dry weight body composition and characteristics on measurement day<sup>a</sup>.

		All patients (n = 54)	Ward patients (n = 30)	ICU patients (n = 24)	p- value
<b>Timeline</b>					
Time from hospital admission to measurement, median [IQR], days		4 (2–11)	3 [2–4]	11 [6–19]	<b>0.000</b>
<b>Clinical characteristics</b>					
SOFA score, median [IQR]		2 [1–4]	1 [1–2]	3 [1–5]	<b>0.009</b>
Temperature, °C		37.3 (37.0–37.5)	37.1 (36.8–37.5)	37.4 (37.0–37.8)	0.323
<b>Physical characteristics</b>					
	<b>Reference value (SE)</b>				
Height, cm	171.5 (0.3) <sup>b</sup>	174 (171–177)	173 (169–177)	176 (171–180)	0.449
Weight, kg	78 (0.5) <sup>b</sup>	90.3 (84.9–95.6)	87.8 (79.8–95.8)	93.3 (86.1–100.5)	0.310
BMI, kg/m <sup>2</sup>	26.5 <sup>b</sup>	29.7 (28.2–31.1)	29.3 (27.0–31.5)	30.2 (28.4–32.0)	0.518
<b>Dry weight BIA-values</b>					
	<b>Reference range/reference value (SE)</b>				
Dry weight, median [IQR], kg <sup>d</sup>	78 (0.5) <sup>b</sup>	85.6 [74.7–101.0]	84.3 [72.4–97.8]	91.0 [77.3–105.2]	0.240
Fat Mass, kg	9.1–17.7 <sup>c</sup>	29.7 (25.9–33.6)	31.40 (25.4–37.4)	27.64 (22.8–32.5)	0.338
Percentage Body Fat (PBF), % <sup>d</sup>	10.0–20.0 <sup>c</sup>	32.8 (29.6–36.0)	35.0 (30.4–39.5)	30.1 (25.5–34.7)	0.135
Fat Free Mass (FFM), kg <sup>d</sup>	51.0–62.3 <sup>c</sup>	59.2 (55.4–63.1)	55.5 (50.7–60.3)	63.9 (57.8–70.0)	<b>0.028</b>
Soft Lean Mass (SLM), kg <sup>d</sup>	48.1–58.7 <sup>c</sup>	55.9 (52.3–59.5)	52.4 (47.9–56.9)	60.3 (54.6–66.1)	<b>0.028</b>
Total Body Water (TBW), ℓ	37.4–45.8 <sup>c</sup>	44.7 (41.8–47.6)	41.5 (38.1–45.0)	48.7 (44.0–53.3)	<b>0.013</b>
Intracellular Water (ICW), ℓ	23.2–28.4 <sup>c</sup>	26.9 (25.2–28.7)	25.2 (23.0–27.4)	29.1 (26.3–31.9)	<b>0.027</b>
Extracellular Water (ECW), ℓ	14.2–17.4 <sup>c</sup>	17.8 (16.6–18.9)	16.3 (15.1–17.6)	19.6 (17.7–21.5)	<b>0.004</b>
Visceral Fat Area (VFA), cm <sup>2</sup>	<100 <sup>d</sup>	155.2 (136.1–174.2)	162.9 (133.6–192.2)	145.5 (121.3–169.7)	0.368
Skeletal Muscle mass Index (SMI), kg/m <sup>2d</sup>	6.77–8.37 <sup>e</sup>	8.0 (7.6–8.4)	7.5 (7.1–8.0)	8.6 (7.9–9.2)	<b>0.006</b>
Fluid overload, ℓ	0 <sup>d</sup>	1.3 (1.0–1.6)	0.9 (0.6–1.2)	1.8 (1.3–2.2)	<b>0.001</b>
ECW/TBW, ℓ	0.36–0.39 <sup>d</sup>	0.40 (0.39–0.40)	0.39 (0.39–0.40)	0.40 (0.40–0.41)	<b>0.015</b>
50 kHz Whole Body Phase Angle, °	5.6–6.5 <sup>f</sup>	4.5 (4.2–4.8)	4.8 (4.4–5.2)	4.1 (3.8–4.5)	<b>0.017</b>

Abbreviations: ICU, Intensive Care Unit; SE, standard error; BMI, Body Mass Index; IQR, interquartile range.

Subheadings and significant results  $p < 0.05$  are in bold.

<sup>a</sup> Data are presented as mean and 95% - confidence interval unless otherwise reported.

<sup>b</sup> Population reference values for men and women in the age range 65–75 years, based on Dutch public records of 2019 [33].

<sup>c</sup> Whenever available, a population mean of the personalized minimal and maximal ideal measurements provided by the Inbody S10 device were given for each body composition value.

<sup>d</sup> Values that are derived from TBW or ECW were recalculated with a healthy ECW/TBW of 0.38 to obtain dry weight values. Healthy reference value or range as provided by Inbody.

<sup>e</sup> Mean SMI for healthy white women resp. men ages 67 years as shown by Lee et al. [31].

<sup>f</sup> Pooled mean phase angle for healthy white women resp. men aged 59–69 years in a meta-analysis by Mattiello [32].

**Table 3**  
28-day outcome and discharge destination<sup>a</sup>.

	All Patients (n = 54)	Ward patients (n = 30)	ICU patients (n = 24)	p- value
<b>Length of stay</b>				
Hospital-free days, median [IQR], days	13 [2–21]	21 [16–23]	2 [0–8]	<b>0.000</b>
<b>Complications<sup>b</sup></b>				
Total	28 (51.9%)	10 (33.3%)	18 (75.0%)	<b>0.002</b>
Mortality	8 (14.8%)	5 (16.7%)	3 (12.5%)	0.720
Thrombo-embolic event <sup>c</sup>	13 (24.1%)	3 (10.0%)	10 (41.7%)	<b>0.007</b>
Renal failure <sup>d</sup>	1 (1.9%)	0 (0.0%)	1 (4.2%)	0.444
Delirium	13 (24.1%)	2 (6.7%)	11 (45.8%)	<b>0.001</b>
Other complications <sup>e</sup>	4 (7.4%)	0 (0.0%)	4 (16.7%)	<b>0.034</b>
<b>Hospital discharge destination</b>				
Other hospital	2 (4%)	0 (0%)	2 (8%)	0.193
Private home	29 (54%)	21 (70%)	8 (33%)	<b>0.007</b>
Rehabilitation facility/nursing home	17 (31%)	5 (17%)	12 (50%)	<b>0.009</b>
In-hospital death <sup>f</sup>	6 (11%)	4 (13%)	2 (8%)	0.682

Abbreviations: ICU, intensive care unit; IQR, interquartile range; no., number.

Subheadings and significant results  $p < 0.05$  are in bold.

<sup>a</sup> Data are presented as median no. of patients (%) unless otherwise reported.

<sup>b</sup> Percentages do not add to 100% as some patients had multiple complications.

<sup>c</sup> Comprised of stroke, pulmonary embolism and deep venous thrombosis.

<sup>d</sup> Renal failure was only scored when requiring new renal replacement therapy.

<sup>e</sup> Only pressure sores following prone ventilation were recorded.

<sup>f</sup> Some patients died within 28-days, but after hospital discharge to elsewhere.

protective and associated with greater survival [22,23]. By measuring BIA body composition, we used a more precise method to study associations between increased body fat mass and visceral fat area and disease severity in COVID-19 patients.

Remarkably, we did not find differences in body composition between COVID-19 ward and ICU patients. Patients had a mean BMI of 29.7 kg/m<sup>2</sup> and a mean age of 67 years. Our cohort comprised 63% men, in keeping with other studies showing higher hospitalization rates amongst men [1,3]. According to national data, in 2019 the average BMI of persons between the age of 65 and 75 years in the Netherlands was 26.5 kg/m<sup>2</sup>. Our cohort is more overweight than the general population [33]. This trend of higher BMI and hospitalization is concordant with other publications [7,9]. Although ICU patients showed a higher BMI (30.2 kg/m<sup>2</sup>) compared with ward patients (29.3 kg/m<sup>2</sup>), this difference was not significant. This contrasts with findings of retrospective studies that showed correlations between increased BMI and ICU admission for COVID-19? [39].

Expectedly, we found that the SOFA-score, an indicator of disease severity, was strongly associated with ICU-admission. Additionally, plasma CK at hospital admission was significantly increased in the eventual ICU-group. This was also observed in a cohort of COVID-19 patients in Wuhan, China [40]. Other possible biomarkers upon hospital admission such as ferritin, CRP, and D-dimer were not-significantly more elevated in ICU patients, although the number of observations were low. No other baseline characteristics were associated with ICU-admission.

Our data demonstrate the potential of PA as a predictor for disease severity in COVID-19 patients. PA has been repeatedly proven to predict morbidity and mortality in other patient groups [41,42,45]. We found no correlations between body composition values and disease severity. A single-center, retrospective study assessing the association between computer tomography-based measurements of visceral fat area and COVID-19 severity found a positive correlation [46]. However, this study was conducted among 30 patients, of whom only 13 were admitted to the ICU. Disease severity was defined as need for ICU admission and invasive mechanical ventilation, and morbidity and mortality were not considered. Thus, both the power and comparability to our study are limited.

We encountered no issues in performing BIA measurements during this study. Nevertheless, we recognize that logistical (time, training) or physical barriers (pulse oximeters, bandages) can potentially complicate (routine) BIA measurements, especially in a busy ICU environment. Other bedside techniques to evaluate muscle mass and quality are available, but come with their own limitations. Muscle ultrasound can be useful to measure muscle quality, quantity and the pennation angle, but performing ultrasound reliably requires training and practice and is potentially susceptible to intra- and inter-observer variability [43,44]. BIA is quick and requires only basic training, adding to the feasibility of use of the technique in the ICU. However, interpretation of the results must be done with caution as discussed below.

#### 4.1. Limitations and considerations

Under challenging conditions, we were able to assess body composition in COVID-19 patients. However, there are several limitations. Firstly, the sample size of 54 can be considered small. In-hospital mortality was low (n = 8,14.8%). Therefore, this cohort may yield insufficient power. A composite score was created to decrease the chance of type 1 error and to obtain a more encompassing definition of the disease course. Despite a robust retrospective basis for the visceral fat distribution hypothesis, we could not find associations between fat mass or distribution and disease severity. If our results prove reproducible, this could influence the direction of research for obesity and COVID-19.

Secondly, 13 (43%) of our ward patients had LTP, waiving ICU admission regardless of disease severity. However, sensitivity testing, yielded no different results. Therefore, we consider that potential selection bias for ICU admission based on perceived health or projected survival chances did not strongly influence our main findings.

Additionally, the most recently measured weight was used as input for the Inbody S10. Daily weight measurements were not always feasible in the ward patients during the pandemic. However, in this study population, the weight measurement was taken less than 48 h prior to the BIA measurement. We therefore do not suspect this to be of significant influence on the results of this study.

**Table 4**  
Multiple regression analysis of dry weight BIA values for different outcome variables<sup>a</sup>.

BIA variables	Odds ratio <sup>b</sup>	p-value
<b>Outcome: ICU admission<sup>c</sup></b>		
Fat Free Mass (FFM/LBM), kg	1.135	0.214
Soft Lean Mass (SLM), kg	1.144	0.212
Skeletal Muscle mass Index (SMI)	4.524	0.087
Total Body Water (TBW), ℓ	1.225	0.126
Intracellular Water (ICW), ℓ	1.324	0.207
Extracellular Water (ECW), ℓ	1.808	0.078
Fluid overload, ℓ	45.408	0.059
ECW/TBW	Infinite	0.089
50 kHz Whole Body Phase Angle, °	0.000	0.130
<b>Outcome: Mortality<sup>c</sup></b>		
Fluid overload, ℓ	3.608	<b>0.043</b>
ECW/TBW	Infinite	<b>0.028</b>
50 kHz Whole Body Phase Angle, °	0.208	<b>0.025</b>
<b>Outcome: Complications<sup>c</sup></b>		
Total Body Water (TBW), ℓ	1.068	0.318
Extracellular Water (ECW), ℓ	1.199	0.248
Fluid overload, ℓ	1.558	0.226
ECW/TBW	Infinite	0.218
50 kHz Whole Body Phase Angle, °	0.413	0.061
<b>Outcome: Composite score<sup>c</sup></b>		
Percentage Body Fat (PBF), %	0.911	0.119
Fat Free Mass (FFM/LBM), kg	1.050	0.411
Soft Lean Mass (SLM), kg	1.053	0.413
Total Body Water (TBW), ℓ	1.070	0.383
Intracellular Water (ICW), ℓ	1.103	0.447
Extracellular Water (ECW), ℓ	1.205	0.315
Fluid overload (FO), ℓ	1.817	0.325
ECW/TBW	Infinite	0.249
50 kHz Whole Body Phase Angle, °	0.299	<b>0.046</b>
<b>Outcome: Vasopressor-free days<sup>d</sup></b>		
Percentage Body Fat (PBF), %	1.004	0.173
Visceral Fat Area (VFA), cm <sup>2</sup>	1.000	0.350

Abbreviations: BIA, bioelectric impedance analysis; ICU, intensive care unit; kHz, kilohertz.

Subheadings and significant results  $p < 0.05$  are in bold.

<sup>a</sup> BIA values were entered in a regression model with the specified outcome variable and the covariates age, sex, SOFA score at admission and days between hospital admission and measurement.

<sup>b</sup> The odds ratio represents the expected increase in the outcome measure upon an increase of 1 unit of the relevant BIA variable.

<sup>c</sup> BIA values entered in a multiple logistic regression model.

<sup>d</sup> BIA values entered in a Poisson regression model, ICU patients only ( $n = 24$ ).

Lastly, the cross-sectional nature of the BIA measurements complicates inter-individual comparability. As both disease and treatment influence body composition, mainly through loss of LBM and increase of fluid overload, differences in time-to-measurement are an important consideration [47,48]. In particular, for ICU patients, in whom fluid overload is common and has prevented BIA measurements from becoming a standard of practice. However, we circumvented this problem by using a multi-frequency BIA device (InBody S10), to enable differentiation between various fluid compartments [28,49,50], adjustment for the time from hospital admission to measurement, and recalculation of body composition to dry weight to reduce the effect of overestimating LBM by fluid overload. We recognize that under ideal circumstances, serial BIA measurements provide more details on the course of loss of muscle mass and fluid overload in critically ill patients.

The method to recalculate BIA parameters to dry weight is based on the assumption that absolute fluid overload is defined as the difference between the measured ECW and the expected ECW under physiological conditions, in which ECW/TBW is estimated to be 0.38 [25,26,28,51–53]. This method has not been validated

in ICU patients; however, it is incorporated in the 'dialysis mode' of the device, a validated method to determine dry weight in dialysis patients. This adjustment method is based on the assumption that fluid overload is exclusively located in the extracellular compartment and questions have been raised as to whether this is an oversimplification in prolonged or severe edema [54]. Likely, there is some muscle cell swelling (ICW) in severe edematous states, leading to overestimation of muscle mass [25,54]. This may explain trends towards higher FFM, SLM, and SMI in the ICU group. Nevertheless, no substantial impact of cell swelling on fat mass and visceral fat area can be expected. Therefore, we are confident that main findings persist. Moreover, additional calculations to estimate fluid overload are useful, as various studies have shown correlations between BIA derived fluid overload and outcome of disease [49,55,56]. The PA is calculated directly from reactance and resistance and is therefore less directly influenced by fluid overload, although theoretically, rapid fluid shifts can contribute to cell damage and, therefore, decrease PA [22]. In practice, PA indeed seems to vary with hydration. However, it remains a good indicator of clinical outcome, as fluid overload itself also negatively impacts outcome of disease, as was suggested by our findings [41,42,57].

## 5. Interpretation

We assessed body composition using BIA in COVID-19 patients and compared ward and ICU patients. Our cohort was overweight, although this was not related to disease severity. Interestingly, we found no significant associations between fat mass or distribution, or fat-free mass and the severity of illness as reflected by ICU admission, complications or mortality. A low phase angle increased the odds of morbidity and mortality in COVID-19 patients. Cautious interpretation of BIA values is warranted in critically ill patients and correction for fluid overload should be performed. Nevertheless, we have shown that BIA measurements in COVID-19 patients are feasible and provide new levels of insight into body composition and phase angle beyond classical anthropometric data such as BMI. As we did not find associations between body composition and disease severity in COVID-19, we believe that other factors may play a more critical role in the development of severe COVID-19.

## Author contributions

HM contributed in conception, data collection, writing and revision of the manuscript. FvZ performed BIA measurements and contributed in data collection, and revision of the manuscript. LD contributed in data analysis and revision of the manuscript. VdS contributed in data collection and revision of the manuscript. RS contributed in data collection and revision of the manuscript. MM contributed in data analysis and revision of the manuscript. AvZ contributed in conception, writing and revision of the manuscript.

## Financial disclosure

None to declare.

## Conflict of interest

Prof. Dr. Van Zanten reported having received honoraria for advisory board meetings, lectures, research, and travel expenses from Baxter, BBraun, Cardinal Health, Danone-Nutricia, Fresenius Kabi, Mermaid, Lyric, and Nestlé-Novartis. The other authors have nothing to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2020.10.023>.

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