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Original article

Bioelectric impedance body composition and phase angle in relation to 90-day adverse outcome in hospitalized COVID-19 ward and ICU patients: The prospective BIAC-19 study

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SUMMARY

Background & aims: Gaining insight into readily obtainable baseline characteristics that allow prediction of adverse outcome in COVID-19 aids both treatment and healthcare planning. Bioelectric impedance (BIA) Phase Angle (PhA) is correlated with outcome in a multitude of diseases and may be of added value in predicting adverse outcome of COVID-19. We aimed to associate baseline body composition parameters with 90-day adverse outcome of COVID-19 including ICU-admission and to explore the added predictive value of baseline PhA.

Methods: We performed a prospective observational study, conducting BIA amongst COVID-19 patients within 24 hours of hospital admission, with a follow-up of 90 days. Data were compared between ward-only and ICU-patients. Regression models were used to assess the associations between baseline characteristics, body composition and 90-day adverse outcome, including a composite outcome score of morbidity, ICU-admission, and mortality. An ROC-curve was used to explore the added predictive value of PhA to other clinical parameters at baseline for the prediction of adverse outcome.

Results: One-hundred-and-fifty patients were included. Mean age was 68 (66–70) years, 67% were male. Forty-one (27%) patients were admitted to ICU and 77 (51%) met the criteria of the composite outcome score. In multiple regression, PhA was independently, inversely correlated with risk of ICU-admission (OR .531, p = .021), complications (OR .579, p = .031), hospital length of stay (OR .875, p = .037) and the composite outcome score (OR .502, p = .012). An ROC-curve showed that the incorporation of PhA in a composite risk-score improved the discriminative power for the composite outcome from poor to fair, compared to individual predictors (AUC 0.79 (95% CI 0.71–0.87)).

Conclusion: BIA measurements including Phase Angle are independently correlated with an adverse outcome of COVID-19. Interpretation of Phase Angle can be a valuable addition to risk assessment of adverse outcome of COVID-19 at hospital admission.

Clinical Trial Registration: Netherlands Trial Register number NL8562, registered 2020-04-21.

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1. Introduction

Since their appearance in late 2019 SARS-CoV-2 and the related Corona Virus Disease-2019 (COVID-19) have challenged healthcare infrastructure worldwide. Much scientific effort has gone into uncovering baseline characteristics that allow for adverse outcome prediction and thereby estimation of healthcare requirements, such as intensive care unit (ICU) capacity. Ideally, risk-scores are composed of measurements and characteristics that are readily

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List of abbreviations

BCa	bias-corrected and accelerated bootstrap
BIA	bioelectric impedance analysis
BMI	body mass index
CI	confidence interval
CK	creatinine kinase
COVID-19	Corona Virus Disease-2019
CRP	C-reactive protein
ECW	extracellular water
ER	emergency room
FFM	Fat-free mass
FO	Fluid overload
HLOS	hospital length of stay
ICU	intensive care unit
ICW	intracellular water
LOS	length of stay
LTP	limited treatment plan
PhA	(50 kHz whole 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

available and correlate with outcome from an early stage disease development.

Obesity is suggested to be a predictive characteristic. However, in a previously published cross-sectional observational cohort study amongst 54 hospitalized COVID-19 patients we found no associations between body mass index (BMI), fat mass, visceral fat area (VFA) and other body compositions parameters as measured by bioelectric impedance analysis (BIA) and adverse outcome of COVID-19 once patients are hospitalized [1]. Interestingly, we did find that Phase Angle (PhA) was inversely related to the odds of adverse outcomes at 30 days, similar to findings in a variety of other diseases.

The PhA reflects the relationship between the reactance and resistance (together called impedance) of the body. These electrical properties can be measured with a BIA device, by attaching four electrodes to the extremities and conducting a brief measurement, similar to obtaining an electrocardiogram. Phase angle is regarded a biological marker of cellular health, as high cell mass volume and robust cell membranes cause delayed signals and thereby a higher PhA. A PhA greater than 6 is assumed healthy, although the normal range varies with sex and age. Diminished cell count, membrane integrity and altered hydration status in critical illness leads to a decreased PhA, which has been shown to correlate with increased mortality, length of ward-, ICU- and hospital-stay, duration of mechanical ventilation and APACHE-II score in various diseases [2].

Recently, Cornejo-Pareja et al. [3] showed that a PhA <3.95° at hospital admission was a significant predictor of 90-day mortality risk independent of age, sex, BMI, and comorbidities in their cohort of 127 hospitalized COVID-19 patients.

As PhA is quick and easy to obtain in virtually all patients, it can be a valuable addition to other clinical parameters in assessing an individual's risk of severe course of disease, if these initial findings can be solidified.

With this prospective continuation of our research, we aim to assess the correlation between baseline PhA and 90-day adverse outcome of COVID-19, in addition to the derived BIA parameters of body composition. Furthermore, we explore the value of the addition of PhA to other baseline clinical characteristics that are readily available at hospital admission, and that aid in the prediction of the disease course.

2. Materials & methods

2.1. Study setting

This prospective observational study was performed at Gelderse Vallei Hospital, a teaching hospital in Ede, The Netherlands. The hospital has two ICU units, with a combined capacity of 18 beds. Thirty-eight general ward COVID-19 beds were available. Early dexamethasone administration was protocol in all COVID-19 patients. Between October 1st and November 19th of 2020, the ICU units participated in the REMAP-CAP trial, after which tocilizumab (RoActemra®) became standard of care for COVID-19 in February 2021 [4]. The hospital did not participate in other interventional trials during the study period.

2.2. Study design and participants

A cross-sectional version of the BIAC-19 study was conducted amongst 54 hospitalized COVID-19 patients between April 10th, and 17th, 2021, of which the results have been published previously [1]. When the second 'wave' of COVID-19 hospital admissions in the Netherlands commenced in October 2020, the ethics board approved a restart of the BIAC-19 with a prospective design. Written informed consent was obtained from all patients or their legal representatives. The study protocol is registered in the Netherlands Trial Register (number NL8562).

Between October 12 and February 10 2021, all patients aged 18 years or above, admitted to the hospital on weekdays with COVID-19 symptoms and who proved PCR-confirmed SARS-CoV-2 positive within 24 hours after hospital admission, were eligible for inclusion. Patients were not considered if they were admitted outside working hours, as the researchers were not present to perform the BIA measurements within 24 hours. In addition, patients were not included if a current SARS-CoV-2 infection was not confirmed within 24 hours after admission, nor if they had been transferred in from another hospital. Exclusion criteria were pregnancy, presence of electrical implants, wounds or skin damage at the designated electrode sites, or inability to maintain posture for 5 minutes.

Patients previously included in the cross-sectional analyses, who had their measurement within 24 hours of hospital admission, were reconsidered for the current analysis.

2.3. BIA measurements

BIA measurements were conducted by trained researchers with the InBody S10® (InBody Co., Ltd., Seoul, Korea). This multi-frequency, segmental impedance analyzer requires height, weight, and sex as input parameters. Height and weight as measured upon admission were used. When circumstances did not allow measurements, height as provided by the patient or representative was entered. BIA measurements were performed in supine position with reusable electrodes attached to the left and right

thumb and middle finger and both ankles. The measurements typically took 3–5 min.

The InBody S10 measures impedance at multiple frequencies and determines a 50 kHz whole body Phase Angle (PhA). Furthermore, segmental measurements are used to calculate total body water (TBW) and (segmental) extracellular water (ECW). Henceforth, the software uses validated methods to estimate fat-free mass (FFM), soft lean mass (SLM), mineral mass, bone mineral content (BMC), percentage body fat (PBF), VFA, skeletal muscle mass (SMM), body cell mass (BCM) and protein mass, in addition to several ratios and segmental values. Fluid overload (FO) was calculated by subtracting a recalculated ECW based on a normal ECW/TBW ratio of 0.380 from the measured ECW (i.e., $OH = ECW_{measured} - ((ICW \times 0.380)/0.620)$), a method that is used in dialysis patients [1,2].

2.4. Data collection

Demographic 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, limited treatment plans (LTP; such as do not resuscitate or no ICU-admission orders), treatments and outcome measures.

Whenever included patients were transferred to another hospital within the same admission period, outcome data were provided upon request by the treating physician of that hospital.

2.4.1. Disease severity scoring

Admission sequential organ failure assessment (SOFA) scores were calculated based on the parameters available from the emergency room (ER) records. As no patients had mechanical ventilation upon admission, fraction of inspired oxygen was calculated based on oxygen delivered by nasal cannula, where open-mouth breathing was presumed for all patients [5]. Missing values were presumed normal, i.e., 0 points added to the patient's SOFA-score.

As SOFA-score is traditionally used in the ICU and not readily available in the ER, respiratory rate (RR) was recorded as an alternative indication of disease severity in COVID-19.

2.4.2. Outcome measures

Adverse outcome was defined in multiple ways. First, ICU-admission for severe COVID-19, and 90-day mortality and other complications were considered. Expected complications were thrombo-embolic events, renal failure, and delirium. Other complications were considered when occurring twice or more in the study population. Additionally, a composite outcome score of ICU-admission and complications, including 90-day mortality, were 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.

Furthermore, hospital length of stay (HLOS), ICU-LOS and hospital discharge destination was recorded. For the ICU-patient group, duration of ventilation and vasopressor use were considered continuous outcome measures related to disease severity.

2.5. Statistical analysis

Normality of the distribution of continuous data was visually assessed by the quantile–quantile plots. Continuous values are reported as mean (95% bias-corrected accelerated bootstrap confidence intervals (95% BCa CI)), discrete data are presented as numbers (%). Patients who had to be admitted to the ICU were compared to ward-only patients. Differences 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 were used. For non-binary categorical data (i.e., discharge destination) analysis of variance was used.

2.5.1. Predictive modeling

Simple regression analysis was performed for associations between baseline characteristics, body composition and outcome of disease. For binary outcomes, binary logistic regression was used. When conditions for linearity of the logit were not met, transformation was performed. Continuous outcomes were univariately analyzed by negative binomial regression with estimated over-dispersion. In all analyses regarding BIA values, age and sex were added into the model to correct for systematic population differences. For binary outcomes that included ICU-admission, patients with an LTP waiving ICU-admission were excluded from the analyses. For outcomes relating to ICU stay, only ICU-patients were considered.

Multiple logistic regression analysis was performed with an enter method for binary outcomes and BIA values with a p-value $\leq$0.10 in simple regression analysis. For continuous outcomes negative binomial regression was used. Unstandardized beta's (B) with their 95% BCa CI are presented. The adjusted odd ratio (Exp(B)) with its 95%-CI is expressed for a 1-point increase in the predictor. Nagelkerke's R-squared was used to interpret goodness of fit of the logistic regression models. Covariates were age, sex and SOFA-score. Analyses were repeated with RR per minute as a substitute for SOFA-score.

We computed a composite predictive risk-score for the composite outcome score, including sex, age, PhA and RR adjusted for their multiple logistic regression odds-ratios. The risk-score was used in ROC analysis with nonparametric distribution assumption to visually compare its discriminative power for the composite outcome score to the continuous predictors alone. The PhA was inverted (1-PhA), as it alone was inversely related to outcome. The discriminative power of the AUC was classified as follows: $0.90 \leq$ AUC $\leq$1.0, excellent; $0.80 \leq$ AUC <0.90, good; $0.70 \leq$ AUC <0.80, fair; $0.60 \leq$ AUC <0.70, poor; $0.50 \leq$ AUC <0.60, failure.

IBM SPSS statistics 27 (IBM Corp, Armonk, NY, USA) was used for all analyses. Only two-sided analyses were used. P-values $\leq$0.05 were considered statistically significant. P-values are reported to a single significant figure unless $0.2 \geq P \geq 0.01$, in which case two significant figures are shown.

3. Results

Between October 10, 2020, and February 11, 2021, 486 patients with PCR confirmed COVID-19 were admitted to our hospital. Of these, 179 patients were screened for inclusion, BIA measurements or PCR could not be performed within 24 h of admission (Fig. 1). One patient declined participation; 28 patients were excluded because of contraindications. Five patients from the previous cross-sectional study were eligible for the prospective analysis based on the revised inclusion criteria [1]. In total, 150 COVID-19 patients were measured and analyzed.

All the included patients were white of Western-European descent. Forty-one (27%) patients eventually had to be admitted to the ICU. Table 1 summarizes baseline characteristics and measurements, and compares those of eventual ICU-patients to ward-only patients. At admission, eventual ICU-patients had higher SOFA-scores, RR, CRP and CK levels, and lower CFS-scores and lymphocytes, than ward-only patients.

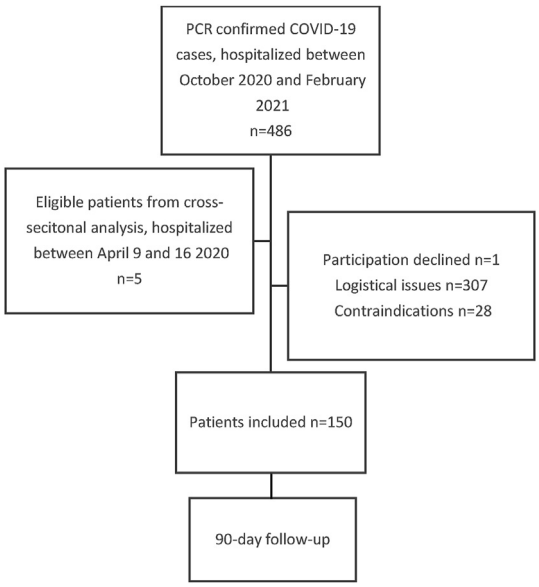

Fig. 1. Study flow diagram.

The unstandardized body composition parameters, including PhA, are shown in Table 2 [6–8]. The 90-day outcome is summarized in Table 3. Of the 11 (10%) ward-only patients who died, seven (70%) had LTP's preventing ICU-admission.

ICU-patients had a mean ICU-LOS of 17 days (95%-BCa CI 13–23), during which 23 (56%) were ventilated for 12 days (95%-BCa CI 7–18), of which 16 (70%) in the prone position, for three days (95%-BCa CI 1–4). Vasopressors were used in 24 (59%) patients, for five days (95%-BCa CI 3–7).

3.1. Predictive modeling

Seventy-seven (51%) patients met the criteria of the composite outcome score, while 73 (49%) were not admitted to the ICU and had no complications including 90-day mortality. The simple regression analyses for BIA values (incorporating sex and age) showed several associations with outcome parameters (e-Tables 1–8). Multiple regression analysis was performed for outcomes and BIA values with a p-value $\leq$0.10 in simple regression analysis.

Table 4 summarizes the adjusted odds ratios derived from the multiple regression analyses, with age, sex and admission SOFA-score used as covariates. The composite outcome score yielded a significant inverse association with PhA (OR 0.629, p = .029). Fat-free mass (OR 1.047, p = .033), SLM (OR 1.050, p = .032), TBW (OR 1.066, p = .029), ICW (OR 1.104, p = .041), ECW (OR 1.181, p = .039), BCM (OR 1.072, p = .026) and SMI (OR 1.447, p = .041) were positively correlated with the chance of ICU-admission. Fat mass (OR .969, p = .021) and VFA (OR .995, p = .050) were significantly inversely associated with complications. ECW/TBW ratio (OR infinitely small, p = .048) was significantly associated with duration of vasopressor use. None of the BIA values were independently associated with ICU-LOS or HLOS.

Table 5 shows these analyses with RR as a substitute for SOFA score as indicator of disease severity. Phase angle remains inversely associated with the composite outcome (OR .502, p = .012), and is newly inversely correlated with ICU-admission (OR .531, p = .021), complications (OR .579, p = .031) and HLOS (OR .875, p = .037). Visceral fat area loses its correlation with complications, as does ECW/TBW-ratio with vasopressor use.

Table 1
Patient characteristics upon hospital admission[a].

	All patients (N=150)[b]	Ward patients (n=109)[b]		ICU patients (n=41)[b]		P- value [c]
Age, years	68 (66-70)	67 (65-70)		68 (66-71)		0.6
Males	100 (67%)	69 (63%)		31 (76%)		0.2
Co- morbidities						
Diabetes	40 (27%)	28 (26%)		12 (29%)		0.7
Hypertension	60 (40%)	45 (41%)		15 (37%)		0.7
Astma/COPD	32 (21%)	23 (21%)		9 (22%)		>0.9
Cardiovascular Disease	43 (29%)	34 (31%)		10 (24%)		0.6
Overweight, BMI 25-30 kg/m^2	67 (45%)	50 (46%)		17 (42%)		0.7
Obesity, BMI >30 kg/m^2	50 (33%)	35 (32%)		15 (37%)		0.7
Clinical scores						
Clinical Frailty score	3 (3)	3 (3)		2 (2-3)		**0.005**
SOFA score	3 (3)	3 (2-3)		4 (4-5)		**0.000**
Respiratory Rate, /minute	25 (24-26)	23 (22-24)	n=106	29 (27 -31)	n=41	**0.001**
Temperature, °C	36.7 (36.6-36.9)	36.8 (36.6 -36.9)	n=108	36.7 (36.5 -36.9)	n=41	0.6
Laboratory results						
Hemoglobin, mmol/L	8.6 (8.4-8.7)	8.6 (8.4-8.8)	n=108	8.5 (8.2-8.8)	n=41	0.5
Leukocytes, 10^9/L	8.1 (7.6-8.6)	7.8 (7.2-8.5)	n=108	8.6 (7.4-9.8)	n=41	0.3
Lymphocytes, 10^9/L	1.1 (1.0-1.2)	1.1 (1.0-1.2)	n=106	0.9 (0.7 – 1.1)	n=41	**0.046**
Thrombocytes, 10^9/L	226 (211-240)	232 (216-250)	n=108	212 (186-237)	n=41	0.2
Ferritin, µg/L	1501 (997-2206)	586 (80-1100)	n=4	1637 (1066-2421)	n=27	0.2
Triglycerides, mmol/L	1.8 (1.5-2.1)	2.0	n=1	1.8 (1.4-2.2)	n=17	0.8
C-reactive protein, mg/L	117 (104-129)	99 (87-111)	n=109	162 (135-190)	n=41	**0.002**
Serum creatinin, µmol/L	100 (90-112)	97 (87-112)	n=107	107 (88-132)	n=41	0.49
Blood urea nitrogen, mmol/L	8.6 (7.6-9.6)	8.1 (7.1-9.1)	n=107	9.8 (7.8-12)	n=41	0.17
Creatinine Kinase, U/L	272 (207-347)	187 (138-252)	n=99	483 (299-706)	n=19	**0.026**
D-dimer, mcg/ml	4.24 (2.23-6.87)	4.06 (1.21-7.80)	n=26	4.43 (1.77-8.19)	n=26	0.9
BUN-to-creatinin-ratio	0.86 (0.81-0.91)	0.08 (0.08-0.09)	n=106	0.09 (0.08-0.11)	n=41	0.12

Abbreviations: ICU, Intensive Care Unit; COPD, Chronic Obstructive Pulmonary Disease; BMI, body mass index; SOFA, sequential organ failure assessment; BUN, blood urea nitrogen.

[a] Data are presented as number (percentage, %) or mean (95% bias-corrected accelerated bootstrapped confidence interval.

[b] Unless otherwise reported, due to missing data.

[c] P-values <0.05 are regarded as statistically significant and displayed in bold.

Table 2
Unstandardized body composition and characteristics on measurement day.[a]

Physical characteristics	Reference value (SE)	All patients (N = 150)	Ward patients (n = 109)	ICU patients (n = 41)	P- value
Height, cm	171 (0.3)[b]	174 (173–176)	174 (173–176)	174 (172–177)	0.9
Weight, kg	78 (0.5)[b]	88 (85–91)	88 (84–92)	90 (86–95)	0.4
Body Mass Index, kg/m^2	26.5[b]	29 (28–30)	29 (28–30)	30 (28–31)	0.4
BIA-values	**Reference range/ reference value (SE)**[c]				
Fat mass, kg	9.6–17.6	30.1 (27.9–32.3)	30.7 (28.2–33.5)	28.3 (24.9–31.8)	0.3
Percentage Body Fat (PBF), %	12.7–22.7	33.2 (31.5–35.0)	34.1 (31.9–36.3)	30.8 (28.0–33.7)	0.07
Fat-Free Mass (FFM), kg	49.5–60.6	58.5 (56.3–60.7)	57.2 (54.8–60.0)	61.8 (58.6–65.0)	**0.026**
Soft Lean Mass (SLM), kg	46.8–57.2	55.1 (53.1–57.2)	53.9 (51.7–56.4)	58.3 (55.3–61.3)	**0.024**
Body Cell Mass (BCM), kg	32.4–39.3	37.7 (36.2–39.2)	36.8 (35.2–38.6)	40.0 (37.8–42.0)	**0.026**
Total Body Water (TBW), ℓ	36.4–44.5	42.9 (41.4–44.6)	41.9 (40.1–43.9)	45.5 (43.2–47.9)	**0.014**
Intracellular Water (ICW), ℓ	22.6–27.6	26.2 (25.3–27.4)	25.8 (24.6–27.0)	27.8 (26.4-29.3)	**0.030**
Extracellular Water (ECW), ℓ	13.8–16.9	16.7 (16.2–17.3)	16.4 (15.7–17.1)	17.7 (16.8–18.6)	**0.013**
Visceral Fat Area (VFA), cm^2	<100[d]	154 (144–166)	160 (146–173)	141 (123–160)	0.095
Skeletal Muscle mass Index (SMI), kg/m^2	6.77–8.37[e]	8.1 (7.8-8.3)	7.9 (7.7–8.2)	8.4 (8.1–8.8)	**0.028**
Fluid overload (FO), ℓ	0	0.59 (0.46–0.73)	0.57 (0.41–0.74)	0.64 (0.41–0.86)	0.6
ECW/TBW, ℓ	0.36–0.39[d]	0.39 (0.39–0.39)	0.39 (0.39–0.39)	0.39 (0.39–0.39)	**0.014**
50 kHz Whole Body Phase Angle, °	5.6–6.5[f]	5.4 (5.2–5.6)	5.4 (5.2–5.7)	5.2 (4.9–5.4)	0.14

Abbreviations: ICU, Intensive Care Unit; SE, standard error.
P-values <0.05 are regarded as statistically significant and displayed in bold.
[a] Data are presented as number (percentage, %), or mean (95% bootstrapped bias correct accelerated confidence interval).
[b] Population reference values for men and women in the age range 65–75 years, based on Dutch public records of 2019 [6].
[c] 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.
[d] Healthy reference value or range as provided by Inbody.
[e] Mean SMI for healthy white women resp. men ages 67 years as shown by Lee et al. [7].
[f] Pooled mean phase angle for healthy white women resp. men aged 59–69 years in a meta-analysis by Mattiello [8].

Table 3
90-day outcome and discharge destinations.[a]

	All Patients (N = 150)	Ward patients (n = 109)	ICU patients (n = 41)	p- value
Length of stay				
Hospital length of stay, days	11 (10–13)	6 (6–7)	25 (20–30)	**0.001**
Complications[b]				
Total	59 (39%)	29 (27%)	30 (73%)	**<0.001**
Mortality	18 (12%)	11 (10%)	7 (17%)	0.3
Thrombo-embolic event[c]	31 (21%)	13 (12%)	18 (44%)	**<0.001**
Renal failure[d]	18 (12%)	8 (7%)	10 (24%)	**0.007**
Delirium	15 (10%)	5 (5%)	10 (24%)	**0.001**
Lung fibrosis	4 (3%)	1 (1%)	3 (7%)	0.06
Hospital discharge destination				
Private home	113 (75%)	92 (84%)	21 (51%)	**<0.001**
Rehabilitation facility/nursing home	22 (15%)	10 (9%)	12 (29%)	
In-hospital death	15 (10%)	7 (6%)	8 (20%)	

Abbreviations: ICU, intensive care unit.
P-values <0.05 are regarded as statistically significant and displayed in bold.
[a] Data are presented as number (percentage, %), or mean (95% confidence interval).
[b] Percentages do not add to 100% as some patients had multiple complications.
[c] Comprised of stroke, pulmonary embolism and deep venous thrombosis.
[d] Renal failure was only scored when requiring new renal replacement therapy.

A composite predictive risk-score for the composite outcome score was calculated with age, sex, PhA and RR adjusted for their multiple logistic regression odd-ratios (Table 6) as: risk-score = (RR × 0.129) + (Age × 0.027) - (PhA × 0.498) + (0.696 if male). The subsequent ROC (Fig. 2) shows that the incorporation of PhA in the composite risk-score improved the discriminative power for the composite outcome as assessed by the AUC from poor (AUC 0.67–0.69) to fair (AUC 0.79 (95% CI 0.71–0.87), compared to individual predictors.

4. Discussion

We aimed to correlate admission BIA body composition with 90-day adverse outcome in 150 COVID-19 patients. After adjusting for age, sex, and disease severity, a lower admission 50 kHz Whole Body Phase Angle at baseline increased the odds of ICU-admission, complications and mortality at 90 days.

Our findings are in line with previous studies, showing correlation between PhA and outcome of disease in multiple patient categories, including COVID-19 patients [1,3,9–12]. Likely, this is explained by the fact that Phase Angle is a reflection the combined effect of premorbid condition, duration and severity of inflammation on cellular quantity and health. However, to ensure interpretation of the association between BIA parameters and outcome of disease independent of severity of disease upon ER presentation, we included SOFA score in our multiple regression analyses and confirmed an independent correlation. Importantly, SOFA score is an ICU instrument and is not routinely calibrated in other settings. Several COVID-19 specific models have been suggested, but none are currently used in our clinical practice. Therefore, we chose to

Table 4
Multiple regression analysis of BIA values for different outcome variables, including age, sex and SOFA score.[a]

BIA variables	B (95%BCa CI)	P-value	OR[b]	95% CI for Odds ratio		Nagelkerke R^2
				Lower	Upper	
Outcome: Composite score[c], n = 127 (no LTP)						
PhA	−0.463 (−0.918, −0.141)	**0.029**	0.629	0.398	0.996	0.324
Outcome: ICU admission[c], n = 127 (no LTP)						
PBF, %	−0.037 (−0.082, −0.005)	0.061	0.963	0.921	1.007	0.384
FFM, kg	0.46 (0.003, 0.108)	**0.033**	1.047	1.000	1.096	0.394
SLM, kg	0.48 (−0.001, 0.109)	**0.032**	1.050	1.000	1.102	0.394
TBW, l	0.064 (−0.001, 0.151)	**0.029**	1.066	1.002	1.134	0.396
ICW, l	0.099 (−0.004, 0.243)	**0.041**	1.104	.999	1.219	0.393
ECW, l	0.166 (0.002, 0.403)	**0.039**	1.181	1.004	1.389	0.395
BCM, kg	0.070 (0.002, 0.161)	**0.026**	1.072	1.000	1.149	0.394
SMI	0.370 (−0.087, 0.928)	**0.041**	1.447	0.962	2.178	0.386
PhA	−0.414 (−1.052, 0.087)	0.12	0.661	0.366	1.194	0.380
Outcome: Complications[c], N = 150						
FM, kg	−0.032 (−0.060, −0.11)	**0.021**	0.968	0.939	0.998	0.283
ECT/TBW, l	3.172 (−14.229, 21.262)	0.7	23.8	0	Infinite	0.250
VFA, cm^2	−0.005 (−0.010, 0.000)	**0.050**	0.995	0.989	1.000	0.275
PhA	−0.397 (−0.814, −0.061)	0.065	0.672	0.427	1.057	0.274
Outcome: HLOS[d], N = 150						
PBF, %	−0.010 (−0.022, 0.001)	0.071	0.990	0.979	1.001	NA
VFA, cm^2	−0.001 (−0.003, 0.000)	0.11	0.999	0.997	1.000	NA
PhA	−0.063 (−0.169, 0.084)	0.3	0.939	0.828	1.065	NA
Outcome: ICU LOS[d], n = 41 (ICU only)						
SMI	−0.076 (−0.380, 0.344)	0.6	0.927	0.749	1.148	NA
Outcome: Vasopressor days[d], n = 41 (ICU only)						
ECW/TBW, l	−18.006 (−43.532, −.003)	**.048**	Infinitely small	Infinitely small	15.7	NA

Abbreviations: BIA, bioelectric impedance analysis; BCa CI, bias-corrected accelerated bootstrap confidence interval; LTP, limited treatment plan; PBF, percentage body fat; FFM, fat-free mass; SLM, soft lean mass; ICW, intracellular water; ECW, extracellular water; TBW, total body water; BCM, body cell mass; SMI, skeletal muscle index; PhA, 50 kHz Whole body phase angle; FM, fat mass; VFA, visceral fat area; HLOS, hospital length of stay; NA, not applicable; LOS, length of stay.
P-values <0.05 are regarded as statistically significant and displayed in bold.
[a] BIA values were entered in a regression model with the specified outcome variable and the covariates age, sex and SOFA score at admission.
[b] The odds ratio represents the expected increase in the outcome measure upon an increase of 1 unit of the relevant BIA variable.
[c] BIA values entered in a multiple logistic regression model.
[d] BIA values entered in a negative binominal regression model.

Table 5
Multiple regression analysis of BIA values for different outcome variables, including age, sex and respiratory rate.[a]

BIA variables	B (95%BCa CI)	P-value	OR[b]	95% CI for Odds ratio		Nagelkerke R^2
				Lower	Upper	
Outcome: Composite score[c], n = 127 (No LTP)						
PhA	−0.689 (−1.219, −0.298)	**0.012**	0.502	0.281	0.898	0.351
Outcome: ICU admission[c], n = 127 (No LTP)						
PBF, %	−0.031 (−0.075, 0.000)	0.132	0.969	0.927	1.013	0.299
FFM, kg	0.049 (.004, 0.110)	**0.018**	1.050	1.004	1.099	0.324
SLM, kg	0.051 (0.002, 0.137)	**0.017**	1.053	1.004	1.104	0.323
TBW, l	0.068 (0.015, 0.138)	**0.004**	1.070	1.007	1.138	0.326
ICW, l	0.103 (0.024, 0.218)	**0.013**	1.108	1.005	1.223	0.321
ECW, l	0.181 (0.027, 0.407)	**0.011**	1.198	1.020	1.407	0.328
BCM, kg	0.072 (0.012, 0.157)	**0.013**	1.075	1.004	1.151	0.322
SMI	0.340 (−0.029, 0.910)	**0.050**	1.405	0.946	2.086	0.307
PhA	−0.632 (−0.1252, −0.267)	**0.021**	0.531	0.285	0.989	0.327
Outcome: Complications[c], N = 150						
FM, kg	−0.029 (−0.062, −0.007)	**0.046**	0.971	0.940	1.002	0.341
ECT/TBW, l	6.497 (0.039, 8.230)	0.4	663.0	0.000	infinite	0.321
VFA, cm^2	−0.004 (−0.010, .000)	0.13	0.996	0.177	1.004	0.333
PhA	−0.547 (−1.104, −0.167)	**0.031**	0.579	0.344	0.973	0.354
Outcome: HLOS[d], N = 150 (ICU only)						
PBF, %	−0.010 (−0.024, 0.003)	0.12	0.990	0.977	1.003	NA
VFA, cm^2	−0.001 (−0.004, 0.001)	0.16	0.999	0.997	1.000	NA
PhA	−0.134 (−0.279, 0.007)	**0.037**	0.875	0.765	1.001	NA
Outcome: ICU LOS[d], n = 41 (ICU only)						
SMI	−0.124 (−0.440, 0.336)	0.5	0.883	0.710	1.098	NA
Outcome: Vasopressor days, n = 41						
ECW/TBW, l	−16.644 (−49.769, 7.651)	0.13	Infinitely small	Infinitely small	234.1	NA

Abbreviations: BIA, bioelectric impedance analysis; BCa CI, bias-corrected accelerated bootstrap confidence interval; LTP, limited treatment plan; PBF, percentage body fat; FFM, fat-free mass; SLM, soft lean mass; ICW, intracellular water; ECW, extracellular water; TBW, total body water; BCM, body cell mass; SMI, skeletal muscle index; PhA, 50 kHz Whole body phase angle; FM, fat mass; VFA, visceral fat area; HLOS, hospital length of stay; NA, not applicable; LOS, length of stay.
P-values <0.05 are regarded as statistically significant and displayed in bold.
[a] BIA values were entered in a regression model with the specified outcome variable and the covariates age, sex and SOFA score at admission.
[b] The odds ratio represents the expected increase in the outcome measure upon an increase of 1 unit of the relevant BIA variable.
[c] BIA values entered in a multiple logistic regression model.
[d] BIA values entered in a negative binominal regression model.

Table 6
Multiple logistic regression of factors associated with the composite score (n = 125).[a]

Variables	B (95%BCa CI)	P-value	OR[b]	95% CI for Odds ratio		Nagelkerke R^2
				Lower	Upper	
Age, years	0.027 (−0.022, .076)	0.02	1.027	0.981	1.076	0.351
Sex (male vs female)	−1.190 (−2.240, −0.350)	**0.019**	0.304	0.110	0.844	
PhA	−0.689 (−1.353, −0.303)	**0.015**	0.502	0.281	0.898	
RR/min	0.121 (0.045, .254)	**0.001**	1.129	1.047	1.217	

Abbreviations: BCa CI, bias-corrected accelerated bootstrap confidence interval; LTP, limited treatment plan; PhA, 50 kHz Whole body phase angle; RR; respiratory rate.
P-values <0.05 are regarded as statistically significant and displayed in bold.
[a] Analysis does not include patients with an LTP preventing ICU admission. In two patients respiratory rate was not recorded upon hospital admission.
[b] The odds ratio represents the expected increase in the outcome measure upon an increase of 1 unit of the relevant BIA variable.

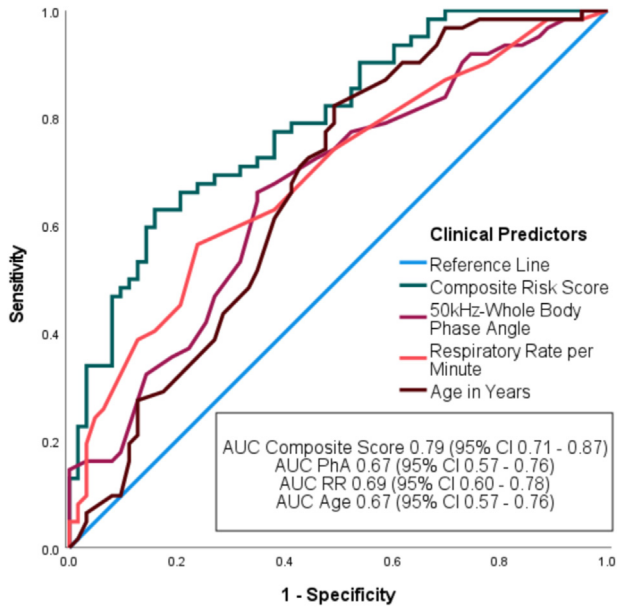

Fig. 2. Receiver operating characteristic (ROC) curve of the diagnostic ability of the individual predictors and the composite risk-score in predicting the composite outcome.

regard respiratory rate as proxy for disease severity. Respiratory rate is a component of the adjusted quick SOFA score and Early Warning Scores that have been validated for use in the ER, and retrospectively related to risk of mortality in elderly COVID-19 patients [13–16]. At baseline, both SOFA score and RR were increased in patients who were eventually admitted to ICU, compared to ward-only patients. Use of RR instead of SOFA score improved the fit of our models whilst increasing significance of the correlation between PhA and all binary outcome parameters.

To explore the added value of baseline PhA to other clinical parameters, a composite risk-score was computed. The addition of PhA improved the discriminative power for the composite of adverse outcome, compared to individual predictors. Based on these results, PhA can and should be considered a valuable component of any future risk-scores concerning COVID-19 and disease course, including ICU-admission. Determination of reference values incorporating age and sex in this population, in order to standardize Phase Angle is the next step in developing an effective and widely applicable risk-score with an effective cut-off value.

4.1. Body composition and outcome

The demographics of our cohort are similar to those found in literature [1,3,12]. Although the average patient was overweight, body mass index was not different between the ICU and the ward-only group, in concordance with our previous findings [1]. This finding further questions the assumption that BMI continues to be related to course of disease in COVID-19 after hospital admission. ICU-patients had increased fat free mass and body water, but lower fat mass, fat percentage and fat area, than ward-only patients. This appears confirmed by the direction of the odds ratios for these parameters and ICU-admission in multiple regression. Nevertheless, the odds ratios for fat, water and lean (fat-free) mass and outcome parameters were each close to one, likely preventing clinical applicability. Similarly, although ECW/TBW was correlated with duration of vasopressor use, the infinitely small odds ratio and its wide 95%-CI negate clinical interpretation based on this sample.

In contrast to our previous cross-sectional research, we did not demonstrate a correlation between fluid overload and adverse outcome. This is most likely explained by the fact that patients had not yet received significant fluid resuscitation, as measurements were performed within 24 hours of hospital admission. Although we previously used correction methods to account for volume overload, we consider baseline measurements as performed in the present cohort methodologically superior.

4.2. Strengths and considerations

There are several strengths to this study. We were able to prospectively include 150 proven COVID-19 patients, which to our knowledge forms the largest published BIA COVID-19 cohort to date. This allowed us to confirm the preliminary results of our cross-sectional study in the same study setting, with improved methodology. Our prospective design allowed BIA measurements to be performed it a protocolled manner, within 24 hours of hospital admission. Hereby, the influence of altered hydration status, an important concern in BIA interpretation, can be considered to be negligible [17].

This study is nevertheless subject to several considerations. During the study period, only 150 (31%) of all admitted COVID-19 patients were considered for inclusion, mainly due to logistical issues. To ensure high internal validity of our results, we only included patients with a PCR-proven SARS-CoV-2 infection in whom all measurements could be performed within 24 hours after hospital admission. Due to laboratory logistics and restricted researcher availability, this meant not all patients could be considered. However, there is no reason to suspect this introduced any patient-related selection bias into the current sample. In addition, issues relating power due to the restricted inclusion are unlikely, as the prevalence of the composite outcome score was 51% in the sample.

It is not uncommon that limited treatment plans are agreed upon at admission of patients of advanced age or with relevant comorbidities. These LTPs prevent admission to the ICU even if the severity of the disease would otherwise dictate it. To prevent

confounding, we did not include LTP patients in analyses regarding the association between clinical characteristics and ICU-admission, including the composite outcome score. This reduced the sample size for these outcomes, although we do not expect this has let the results to be underpowered. In contrast, the analyses regarding the ICU population only included 41 patients, providing a possible explanation for the insignificant results regarding these outcomes.

5. Conclusion

We assessed admission body composition using BIA in COVID-19 patients and correlated it with 90-day adverse outcome, whilst controlling for age, sex and severity of disease. A low Phase Angle significantly, independently increased the odds of ICU-admission, morbidity and mortality. As PhA is easy and quick to determine, it should be considered as an addition to any baseline clinical risk-score. Determination of reference values incorporating age and sex in this population is the next step in developing an effective and widely applicable risk-score with an effective cut-off value.

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Gelderse Vallei Hospital (no. 2004–025). Written informed consent was obtained from all patients or their legal representatives.

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Author contributions

HM contributed to conception, data collection, data analysis and interpretation, writing and revision of the manuscript. AB, AH, ES and FvZ performed BIA measurements and contributed to data collection, and revision of the manuscript. AvZ contributed to conception, data interpretation and revision of the manuscript.

Declaration of competing interest

Prof. Dr. Van Zanten reported having received honoraria for advisory board meetings, lectures, research, and travel expenses from AOP Pharma, Baxter, Cardinal Health, Danone-Nutricia, DIM3, Fresenius Kabi, GE Healthcare, Mermaid, Rousselot, and Lyric. The other authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.10.010.

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