DOI: 10.1002/jpen.2585

ORIGINAL RESEARCH

Association between fat-free mass and survival in critically ill patients with COVID-19: A prospective cohort study

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Abstract

Background: Most critically ill patients with COVID-19 experience malnutrition and weight loss associated with negative clinical outcomes. Our primary aim was to assess body composition during acute and late phase of illness in these patients in relation to clinical outcome and secondary to tailored nutrition support.

Methods: This prospective cohort study included adult critically ill patients with COVID-19. Body composition (fat-free mass [FFM] [exposure of interest], fat mass [FM], skeletal muscle mass [SMM], and phase angle [PA]) was determined with multifrequency bioelectrical impedance analyses in the acute and late phase. Nutrition support data were collected simultaneously. Clinical outcome was defined as ICU survival (primary outcome) and 30–90 days thereafter, duration of mechanical ventilation, and length ICU stay and of hospital stay (LOS). Nonparametric tests and regression analyses were performed.

Results: We included 70 patients (73% male, median age 60 years). Upon admission, median BMI was 30 kg/m^2, 54% were obese (BMI > 30 kg/m^2). Median weight change during ICU stay was −3 kg: +3 kg FM and −6 kg FFM (−4 kg SMM). Body composition changed significantly ($P < 0.001$). Regarding clinical outcome, only low PA was associated with prolonged LOS (odds ratio = 0.83, 95% CI = 0.72–0.96; $P = 0.015$). Patients with optimal protein intake (>80%) during acute phase maintained significantly more FFM (2.7 kg, $P = 0.047$) in the late phase compared with patients who received <80%.

Conclusion: FFM decreased significantly during acute and late phase of illness, but we observed no association with ICU survival. Only low PA was associated with prolonged LOS. FFM wasting likely occurred because of disease severity and immobility.

KEYWORDS
body composition, clinical outcome, COVID-19, critically ill patients, nutritional assessment

INTRODUCTION

The majority of critically ill patients with coronavirus disease 2019 (COVID-19) experience malnutrition and weight loss during hospitalization,[1,2] which negatively impact the patient's outcomes, such as prolonged length of intensive care unit (ICU) stay and prolonged length of hospital stay (LOS).[3–5] The course of critical illness can be divided into several disease phases (the acute, late, and recovery phases), each with its own characteristics and impact on nutrition status with respect to nutrition intake.[6,7] The acute phase lasts up to 7 days after admission and is characterized by metabolic changes, a higher catabolic state, and loss of muscle mass. This phase is followed by the late phase, which is characterized by improvement in inflammation and rehabilitation or by a persistent catabolic state.[6] Finally, the late phase evolves into the recovery phase after leaving the ICU.[6,7]

An extensive decline in muscle mass and function is common during ICU stay.[6] Adequate nutrition support (70%–100% of requirements) during critical illness may reduce this loss,[6] and it is associated with improved clinical outcomes in ICU patients with COVID-19.[4,5] It has been shown that critically ill patients with COVID-19 can be fed adequately with acceptable feeding (in)tolerance during ICU stay.[8,9] Most of these patients, however, were demonstrated to be persistently hypermetabolic[8,10–12] with a negative urinary protein balance in both the acute and late phases.[8] These results indicate that critically ill patients with COVID-19 persist in a catabolic state for an extended period, which may further negatively impact body composition over time (decline of muscle mass).

To evaluate body composition in critically ill patients, multi-frequency bioelectrical impedance analysis (BIA) can be used.[6,13] BIA is an indirect, noninvasive method that determines the impedance of frequencies alternating current through the body. This method determines whole and segmental body weight tissues (fat mass [FM], fat-free mass [FFM], and skeletal muscle mass) and provides information on hydration status and cell membrane integrity (phase angle).[14] FFM consists of skeletal muscle mass, organs, bones, and intracellular and extracellular water.[15] It has been shown that most critically ill patients with COVID-19 also have overweight or obesity,[16,17] with both a high BIA-derived FM and high FFM compared with population reference values.[18] In these patients, low muscle mass and higher FM values are associated with negative clinical outcomes.[3,19]

Until now, no data have been available on the change of body composition in relation to clinical outcome and nutrition intake in patients with COVID-19 during ICU stay. More insight into this change in relation to clinical outcome and nutrition intake is important for designing effective nutrition support strategies to improve a patient's outcome. Therefore, our primary aim is to assess body composition during the acute and late phases of critical illness in patients with COVID-19 in relation to clinical outcome. Our secondary aim is to assess the relation between body composition and tailored nutrition support. We hypothesize that a decrease in estimated FFM is associated with decreased ICU survival in patients with COVID-19.

MATERIALS AND METHODS

Study population and design

This prospective cohort study was conducted from June 2020 to July 2022 in the Erasmus Medical Centre, Rotterdam, the Netherlands, with approval from the institutional review board (MEC-2020-0336). Mechanically ventilated patients with COVID-19 (>18 years) admitted to the ICU were included. Patients with (1) a metabolic disease requiring a specific diet (eg, phenylketonuria), (2) (home) parenteral nutrition starting >7 days before admission unrelated to COVID-19, and (3) a pacemaker implant were excluded. Pregnant women and patients with no BIA measurement in both phases were excluded from analyses. Patients who were already admitted in other hospitals and were referred to our tertiary hospital because of progression of disease severity were considered to be in the acute phase upon admission. Data on patient characteristics and nutrition assessment, including body composition and nutrient balance, were collected. Written informed consent was obtained and data management was performed using Castor Electronic Data Capture, version 2021.1 (Castor EDC).

Patient characteristics

Data on patients' characteristics included age, weight, height, sex, body mass index (BMI), mortality risk (Acute Physiology and Chronic Health Evaluation IV), and comorbidities. Additional variables included illness severity score (Sequential Organ Failure Assessment [SOFA]), body temperature, duration of mechanical ventilation, use of continuous renal replacement therapy, use of COVID-19 drugs (ie, tocilizumab or dexmedetomidine), and whether a patient was transitioned from another ICU.

Body composition

Our exposure of interest was the change in acute and late FFM determined by a multifrequency BIA (InbodyS10, Inbody Co Ltd). FFM was measured via multifrequency BIA in the acute phase (around day 4), late phase (around day 10), and, if applicable, on weekends. Measurements were performed by a trained intensivist (BvH) or critical care dietitian (PL) in a supine position and pertained to standard care. Actual bodyweight (kilograms) was measured with a calibrated weight scale integrated in the ICU bed. Whole-body FFM, FM, skeletal muscle mass, and intracellular and extracellular water were determined and the phase angle was deduced, in which whole-body (50 kHz) phase angle values ≤5° were considered too low.[18,20] In case of fluid overload (ie, extracellular water/total body water ratio >0.385), FFM was corrected to dry weight values using a standardized ratio of 0.380 for healthy persons.[18] Both the FM index and FFM index were calculated and values <10th percentile were considered too low and >90th too high.[21] Skeletal muscle mass index values <7.0 kg/m^2 for men and <5.5 kg/m^2 for women were defined as too low.[22]

Clinical outcome

Our primary outcome was ICU survival (yes/no) determined by a national registry. Secondary clinical outcomes were defined as ICU survival after 30 days (yes/no), ICU survival after 90 days (yes/no), length of ICU stay in days, LOS in days, and duration of mechanical ventilation in days.

Tailored nutrition support

Nutrition data (energy and protein) were collected on the same day as body composition measurement. If applicable, nonnutrition energy (eg, propofol) was taken into account. Data of feeding intolerance included gastric residual volumes (GRV) and diarrhea (Bristol stool scale ≥6).[23] High GRV was defined as at least two times ≥150 ml per day, and gastrointestinal (GI) dysfunction was defined as an acute GI injury grade of at least III.[24] Indirect calorimetry (Q-NRG+, Cosmed, Italy) was used to measure resting energy expenditure (mREE) in accordance to guidelines.[25,26] Predictive formulas were used in case of contraindications for indirect calorimetry (ie, fraction of inspired oxygen >70%) to compare results. Estimation of the total energy requirement was made individually and ranged from 10% to 30%.[8,9] To examine hypometabolism and hypermetabolism, the mREE was compared with the predicted REE (mREE/predicted REE × 100%), in which hypometabolism was defined as <90% and hypermetabolism as >110%. The calculated protein requirement ranged from 1.3 to 1.7 g/kg, taking protein losses into account, with an average of 1.5 g/kg.[6,27] The actual measured bodyweight (kilograms), if indicated as corrected for fluid overload, was used to determine optimal nutrition requirements.[8,9] Optimal tailored nutrition support was defined as >80% of the nutrition requirement received. In accordance to our nutrition protocol, enteral nutrition was started 24–48 h after admission via nasogastric tubes and feeding was gradually increased based on the European Society for Clinical Nutrition and Metabolism guidelines.[6]

Statistical analysis

Normally distributed values were presented as mean (SD) or median (interquartile range [IQR]) and categorical values as numbers (percentages [%]).The change of body composition during the acute and late phases was assessed with a paired samples *t* test in the case of normally distributed data, otherwise a Wilcoxon signed rank test was performed. Differences in the body composition parameters between the phases were also checked for nonnormality.

Regression analyses were performed to determine associations between body composition, clinical outcome, and tailored nutrition support.

The association between body composition parameters and the outcomes ICU stay, LOS, and duration of mechanical ventilation was analyzed using negative binomial regression analyses because this method performed favorably for this data.[28] Changes in body composition parameters (ie, FM, FFM, skeletal muscle mass, FM index, FFM index, skeletal muscle mass index, total body water, intercellular water, extracellular water, and phase angle) between the acute and late phase were used as continuous determinants. Analyses were additionally corrected for the following confounders: sex, age, SOFA score at baseline, presence of any comorbidity (yes/no), BMI, and the time between measurements (days). The time between measurements was defined as the days between the first measurement in the acute phase and the second measurement in the late phase. This is because varying measuring moments may affect the change in body composition. Data were presented as rate ratios (RRs) with 95% CIs. The RR represents the change in the dependent variable in terms of percentage, determined by the amount of the RR, per unit increase of the independent variable.

To model the association between body composition and ICU survival, ICU survival after 30 days, and ICU survival after 90 days, univariable logistic regression analyses were performed. Because of our sample size, we did not include confounders in these analyses. Data were presented as odds ratio with 95% CIs.

Linear regression analyses were performed for the association between tailored nutrition support and body composition (outcome). Homogeneity of variance and other assumptions of linear regression were assessed by inspecting plots of residuals. Tailored nutrition support was analyzed both as a continuous variable (percent intake of requirement) and as a dichotomous variable (less than or >80% of the requirement). Analyses were additionally corrected for the following confounders: sex, age, SOFA score at baseline, presence of any comorbidity (yes/no), BMI and time between measurements (days). A polynomial function form was performed to explore nonlinearity. Data were presented as coefficients.

Power analysis was not performed because of the lack of available published or pilot data needed to determine sample size. Based on the admission rate of patients with COVID-19 as estimated in April 2020, the initial aim was to include at least 100 patients. Data analysis was performed using IBM SPSS statistics for Windows, version 28.0 (IBM Corp), and a two-sided *P* value of <0.05 was considered to be statistically significant.

RESULTS

Study population

Of 81 eligible patients, a total of 70 patients (86%) were measured in both phases and included for analyses. Five patients were measured beyond the selected time frames, five had incomplete BIA data, and one was pregnant. The study population consisted mostly of middle-aged men (Table 1). Upon admission, the median BMI was 30 kg/m^2 (IQR = 26–33), and 54% of the patients were obese (BMI > 30 kg/m^2). Most patients (69%) had at least one comorbidity, in which hypertension was most prevalent (34%) followed by diabetes mellitus type 2 (27%). Multiple comorbidities were present in 27% of the patients. Thirty-three (47%) patients were transferred from another ICU (Table 1). During ICU

TABLE 1 Patient characteristics of the included critically ill patients with coronavirus disease 2019 (*N* = 70).

Characteristics	*N* = 70
Male sex, *n* (%)	51 (73)
Age, median (IQR), years	60 (52–69)
BMI, median (IQR), kg/m^2	30 (26–33)
Underweight, *n* (%)	0 (0)
Normal weight, *n* (%)	12 (17)
Overweight, *n* (%)	20 (29)
Obese, *n* (%)	38 (54)
SOFA score, median (IQR)	6.0 (6–9)
APACHE IV, median (IQR), %	18 (13–30)
Comorbidities, *n* (%)	
One comorbidity	48 (69)
≥2 comorbidities	19 (27)
Transferred from another ICU, *n* (%)	33 (47)
Survival ICU stay, *n* (%)	58 (83)

Note: APACHE IV is expressed as risk (%), in which a higher percentage indicates higher risk of mortality at admission.

Abbreviations: APACHE IV, Acute Physiology and Chronic Health Evaluation IV; BMI, body mass index; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment (score ranges from 0 to 24).

admission, the use of COVID-19 drugs decreased from 23% upon admission to 3% in the late phase. The mean body temperature remained around 37°C during both phases.

CLINICAL OUTCOME

All patients were mechanically ventilated for a median duration of 23 days (IQR = 7–78). A total of 58 patients (83%) survived their ICU stay. Thirty days after ICU admission, 56 patients (80%) were still alive and two patients were lost to follow-up; 90 days after admission, 54 patients (77%) were still alive and four patients were lost to follow-up. The median days spent in the ICU was 26 (IQR = 15–37), and the median LOS was 32 days (IQR = 12–93).

Body composition

The first BIA measurement was performed on median day 4 (IQR = 2–6) and the second on day 10 (IQR = 8–12). Because of medical reasons, not all patients were available for measurements at day 4 and day 10. Median weight loss from the acute phase to the late phase was −3 kg, of which −6 kg were FFM and +3 kg were FM. As presented in Table 2, both body composition and hydration status changed significantly during the acute and late phases (all $P < 0.001$). There was a decrease in FFM and FFM index consisting of −4 kg skeletal muscle mass, −1 kg skeletal muscle mass index, and −5 L total body water, of which −2 L were extracellular water and −3 L intracellular water. FM and FM index increased during admission. Phase angle remained low and did not change significantly ($P = 0.198$). Most patients (83%) had a high FFM index compared with reference values in the acute phase, which decreased to 66% in the late phase ($P < 0.001$). Conversely, the percentage of those with a high FM index increased from 47% to 63% during ICU stay ($P < 0.001$).

Tailored nutrition support

Most patients (98%) were fed with polymeric enteral nutrition during ICU stay. High GRV was observed in a minority of patients and decreased during admission (25%–15%). None of our patients was classified with GI dysfunction. Indirect calorimetry was performed in 58 patients (83%) in both phases. In these patients, mean (±SD) mREE in the acute phase was 1750 kcal (±397), and this increased significantly to 1880 kcal (±444) in the late phase ($P < 0.001$). Concerning metabolism, half of the patients (53% vs 47%) were classified with normometabolism and a minority with hypo- (35% vs 37%) and hypermetabolism (12% vs 16%) in both phases. The median delivery of prescribed energy was 75% (IQR = 51–99) and of protein 60% (IQR = 38–81) in the acute phase, and these increased to 99% (IQR = 87–111) and 95% (IQR = 82–105) in the late phase, respectively. Forty-nine percent of the patients ($n = 34$) received >80% of their energy and 27% ($n = 19$) of their protein goals in the acute phase, whereas this was 85% and 79% in the late phase, respectively.

Body composition and clinical outcome

Because 12 (17%) patients died in the ICU after two BIA measurements, it was not possible to include confounders in the regression analyses for survival. The crude analyses showed no significant associations between changes in body composition parameters and ICU survival, ICU survival after 30 days, and ICU survival after 90 days (Tables S2, S2A, and S2B). Our primary exposure of interest (FFM) showed no significant association with our primary clinical outcome (ICU survival) ($P = 0.350$, OR 0.94 [95% CI = 0.8–1.1]). A lower phase angle was associated with a prolonged LOS ($P = 0.015$, RR 0.8 [95% CI = 0.7–0.9]). Each degree decrease of the phase angle was associated with a 20% increase of LOS. No other adjusted associations were found.

Body composition and tailored nutrition support

When analyzing the data continuously, corrected for confounders, an increase of both the administrated energy and protein intake (+10%) resulted in <1% difference (3 g) of FFM ($P = 0.10$), of which 20 g was skeletal muscle mass ($P = 0.12$) and 50 g was FM ($P = 0.03$) between the acute and late phases. Regarding optimal tailored nutrition

TABLE 2 Change of whole-body composition values measured with bioelectrical impedance analysis between the acute and late phase of critically ill patients with coronavirus disease 2019 ($N = 70$).

Dry weight values[a]	Acute phase,[a,b]	Late phase,[a,c]	Difference in mean/ median[d] (95% CI)	*P* value
Total body weight, mean ± SD, kg	99 ± 19	96 ± 19	−3 (−4 to −2)	**<0.001**
Dry weight, mean ± SD, kg	98 ± 19	95 ± 19	−3 (−4 to −2)	**<0.001**
Fat-free mass, median (IQR), kg	71 (61 to 82)	65 (57 to 74)	−6 (−7 to −5)	**<0.001**
Fat mass, median (IQR), %	28 (21 to 33)	31 (23 to 39)	3 (2 to 4)	**<0.001**
Fat mass median (IQR), kg	27 (18 to 34)	30 (21 to 35)	3 (3 to 5)	**<0.001**
Skeletal muscle mass, median (IQR), kg	40 (33 to 46)	36 (32 to 42)	−4 (−4 to −3)	**<0.001**
Fat-free mass index, median (IQR), kg/m^2	23 (21 to 25)	21 (19 to 23)	−2 (−2 to −1)	**<0.001**
Fat mass index, median (IQR), kg/m^2	9 (6 to 11)	10 (7 to 12)	1 (1 to 2)	**<0.001**
Skeletal muscle mass index, median (IQR), kg/m^2	10 (9 to 11)	9 (8 to 10)	−1 (−1 to −1)	**<0.001**
Total body water, median (IQR), L	53 (45 to 62)	48 (42 to 56)	−5 (−6 to −3)	**<0.001**
Extracellular water, median (IQR), L	21 (18 to 25)	19 (17 to 22)	−2 (−2 to −1)	**<0.001**
Intracellular water, median (IQR), L	32 (27 to 37)	29 (26 to 34)	−3 (−3 to −2)	**<0.001**
Phase angle, median (IQR), degrees	5 (4 to 5)	4 (4 to 5)	−1 (−0.2 to 0.5)	0.198

Note: Bold *P* values are significant.

Abbreviations: CI, confidence interval, IQR, interquartile range; kg, kilogram; L, liter.

[a]Reference (range) values for whole and segmental body composition values are presented in Table S1.

[b]Median day of measurement 4 (IQR = 2–6).

[c]Median day of measurement 10 (IQR = 8–12).

[d]Difference of body composition parameters between the acute and late phase in mean or median with 95% CI.

support, patients receiving >80% of their protein requirement in the acute phase maintained significantly more FFM (2.7 kg, $P = 0.047$) and skeletal muscle mass index (0.5 kg/m^2, $P = 0.049$) and had reduced loss of FM (−4 kg, $P = 0.004$) and FM index (−1 kg/m^2, $P = 0.005$) in the late phase compared with patients who received <80%. Of their protein requirement. Optimal energy intake showed significantly reduced loss of FM (−2.7 kg, $P = 0.043$) and FM index (−0.43 g/m^2, $P = 0.038$). No other adjusted associations were found.

DISCUSSION

To our knowledge, this is the first study assessing the change of body composition in relation to both clinical outcome and tailored nutrition support in critically ill patients with COVID-19. Our study shows a median weight change during ICU stay of −3 kg (sum of −6 kg FFM, of which −4 kg is skeletal muscle mass and +3 kg is FM) in these patients. Low phase angle was associated with a longer LOS, and no other associations were found between body composition and clinical outcome. Optimal protein intake (>80%) in the acute phase was associated with more maintenance of FFM and skeletal muscle mass index and a smaller loss of FM and FM index in the late phase, in which the optimal energy intake (>80%) was only associated with reduced loss of FM and FM index.

Body composition changed significantly in our patients with COVID-19 during the acute and late phases of critical illness. Our study results are consistent with previous studies in general ICU patients[6,28] and show that critically ill patients with COVID-19 also have a large loss of FFM and skeletal muscle mass during their ICU stay. Within the loss of FFM, skeletal muscle mass, intracellular water, and extracellular water decreased. Apparently this phenomenon may be related to critical illness in general and not specific to COVID-19.[6,29] Unlike our hypothesis, the observed decrease of FFM was not associated with decreased ICU survival. This might be due to the small sample size and other factors, such as disease severity and immobility.

Interestingly, we found an increase in FM that has not been reported before in critically ill patients but has been observed in hemodialysis and patients with cancer.[29,30] Despite feeding our patients by our nutrition protocol based on international guidelines and[4,6] guided by indirect calorimetry, the FFM and FFM index decreased during admission whereas the occurrence of a high FM index further increased (63%). This raises the question whether our patients could have been overfed during ICU stay and whether the actual guidelines are appropriate to counteract these unfavorable alterations in body composition in critically ill patients with COVID-19. In addition, the loss of FFM is likely explained by the severity of critical illness or difficulties in delivering nutrition goals.

The goal of adequate nutrition support in critically ill patients is to prevent loss of muscle mass.[6] The majority (73%) did not reach adequate protein intake in the acute phase, most likely because of more severe critical illness and prone positioning during mechanical ventilation. We observed an association between optimal protein intake in the acute phase and more maintenance of FFM and skeletal muscle mass index in the late phase ($P = 0.047$ and $P = 0.049$, respectively).

Previously, it has been shown that providing adequate protein intake in the first week of ICU stay (>1.1 g/kg/day) can bypass the anabolic resistance[31–33] associated with attenuation of muscle mass loss.[32] These results indicate the importance of optimal protein support in the acute phase. However, conflicting data have been reported in which this association was not found.[29,30] Other factors influencing loss of muscle mass, such as prescribed medications (eg, sedatives), inflammation, comorbidities, and early mobilization strategies, should be considered in terms of causal alterations in body composition. Because we were unable to include these influencing factors, the relationship between body composition and optimal protein intake that has been found cannot be interpreted as causal.

Previously, in critically ill patients with COVID-19 persistent hypermetabolism was shown during the first wave (2019–2020) of COVID-19[8,10–12]; however, in this study (2020–2022) the occurrence of hypermetabolism (12% and 16%, respectively) was lower. Because we have performed REE measurements during the different waves of COVID-19 (with different COVID-19 strains) and treatment was altered over time, this might be an explanation for an altered metabolism and, therefore, a lower occurrence of hypermetabolism. The frequent use of indirect calorimetry seems, therefore, essential to monitor (energy) metabolism in combination with BIA to guide adequate tailored nutrition support during admission in favor of patient recovery.

Based on our results, low phase angle was only associated with a longer LOS. Phase angle indicates cellular membrane health and integrity[31,32] and could be used as a prognostic indicator to estimate clinical outcome in critically ill patients.[33,34] A lower phase angle is considered to be a predictor of disease severity[18,35] and is recommended as a marker for nutrition status and mortality risk in the daily practice of patients with COVID-19.[36,37] Our results are in line with other studies[38,39] and, therefore, may support the potential use of phase angle as a marker for LOS in critically ill patients.

Some limitations of this study need to be addressed. First, our sample size was relatively small, which may have led to sparse data bias. Second, the focus of our study was limited to the acute and late phases of disease, and this timeframe might be too short to find associations between body composition and clinical outcome. Third, no correction was made for the number of days a patient stayed in another ICU. Because most patients were transferred within 2 days and the acute phase might be prolonged in patients with COVID-19, this will have little impact on our results. Fourth, mobilization was not considered and, therefore, results regarding FFM should be interpreted with caution. Nevertheless, the study population was homogenous, and measurements were conducted in daily practice during the COVID-19 pandemic.

CONCLUSION

During ICU admission, FFM decreased significantly in our group of patients with COVID-19; however, we observed no association with ICU survival. This decrease may be explained by immobility and by the severity of critical illness, likely causing nutrition problems. Despite a high-quality nutrition protocol, these problems caused nonachievement of nutrition goals in the acute phase. Phase angle might be used as a marker for LOS in these patients. Further intervention studies on the effect of tailored protein and energy support combined with (early) mobilization programs on the maintenance of muscle mass during ICU stay are needed.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the research; Patty L. M. Lakenman and Ben van der Hoven conducted the measurements and calculations; Iris van Marwijk and Patty L. M. Lakenman analyzed the data; and Patty L. M. Lakenman wrote the manuscript. All authors have read, edited, and approved the manuscript.

ACKNOWLEDGMENTS

The authors acknowledge Joost M. van Rosmalen, PhD and Eleni Andrinopoulou, PhD for their help with the statistical analyses.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lakenman PLM, Marwijk I, Hoven Bvd, Bommel J, Joosten KFM, Olieman JF. Association between fat-free mass and survival in critically ill patients with COVID-19: a prospective cohort study. *J Parenter Enteral Nutr*. 2023;1-7. doi:10.1002/jpen.2585