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Original article

Individualised energy and protein targets achieved during intensive care admission are associated with lower mortality in mechanically ventilated COVID-19 patients: The COFEED-19 study

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SUMMARY

Background & aims: Malnutrition is prevalent among COVID-19 patients admitted to the intensive care unit (ICU) and it is associated with poor survival. Customized nutrition plays a vital role in enhancing outcomes for this patient population. This study explores the association between energy and protein intake and 90-day mortality in invasively mechanically ventilated COVID-19 patients, utilizing fat-free mass (FFM) and actual body weight (ABW) for nutritional requirements. Furthermore, the study investigates the occurrence of gastrointestinal (GI) intolerance in critically ill COVID-19 patients in relation to their nutritional intake and survival.

Methods: A retrospective study was undertaken at a university-affiliated teaching hospital, focusing on COVID-19 patients on invasive mechanical ventilation admitted to the ICU between March 2020 and December 2021. The study collected demographic and clinical data, along with cumulative energy and protein goals, and recorded cumulative intake on days 4, 7, and throughout the ICU stay. Univariate and multivariable Cox regression analyses were conducted to evaluate associations between energy and protein deficits and the 90-day all-cause mortality.

Results: The study included 85 patients, of whom 67 (78 %) survived 90 days after ICU admission. There were no significant differences in body composition between survivors and non-survivors. Reaching ≥70 % of the energy goal based on both ABW and FFM during the ICU stay was associated with decreased 90-day mortality (HR 0.22, 95 % CI 0.08–0.60 and HR 0.28, 95 % CI 0.09–0.85, respectively). Similarly, achieving ≥80 % of the protein target based on FFM was associated with decreased 90-day mortality (HR 0.26, 95 % CI 0.07–0.94), whereas no significant association was found for reaching protein targets based on ABW (HR 0.03, 95 % CI 0.00–3.40). Patients who reached both their energy and protein goal based on FFM during ICU admission showed a lower risk of all-cause 90-day mortality compared to those who received <70 % of the energy goal and <80 % of protein based on FFM after adjusting for age (aHR 0.12, 95 % CI 0.03–0.50). No differences in GI intolerance related symptoms between COVID-19 survivors and non-survivors were observed.

Conclusions: This study underscores the significance of providing adequate nutritional therapy to COVID-19 ICU patients who require IMV. Meeting over 80 % of the protein goals based on BIA-derived FFM was associated with lower mortality rates, which emphasizes the need for further investigation into the role of FFM in establishing nutritional targets.

1. Introduction

Coronavirus disease 2019 (COVID-19) can lead to respiratory insufficiency, necessitating invasive mechanical ventilation (IMV) in Intensive Care Units (ICUs) for severe cases. Consequently,

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Abbreviations

ABW	Actual body weight
ASPEN	American Society for Parenteral and Enteral Nutrition
BIA	Bioelectrical impedance analysis
BMI	Body mass index
COVID-19	Coronavirus 2019
EN	Enteral nutrition
ESPEN	European Society for Clinical Nutrition and Metabolism
FFM	Fat-Free Mass
GI	Gastrointestinal
GRV	Gastric residual volume
IBW	Ideal Body weight
IC	Indirect calorimetry
ICU	Intensive care unit
ECW	Extracellular Water
TBW	Total Body Water
IMV	Invasive mechanical ventilation
REE	Resting energy expenditure
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2

enteral nutrition (EN) becomes essential. The composition, timing, and delivery of EN could play a vital role in the survival and recovery of critically ill ICU patients [1,2].

Several recent observational studies have indicated a higher prevalence of nutritional deficiencies among COVID-19 patients during their ICU stay compared to non-COVID-19 critically ill patients [3–5]. Additionally, in a small prospective study, malnutrition was found in approximately 80 % of patients at ICU discharge, with about 50 % of these patients still suffering from malnutrition three months later [6].

There is evidence linking COVID-19 to increased gastrointestinal (GI) intolerance symptoms, which could possibly lead to reduced nutrient absorption [7,8]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acts on enterocyte ACE2 receptors, thereby inducing symptoms of GI intolerance, including anorexia, vomiting, diarrhoea, and abdominal pain [8]. These factors, among others, may make COVID-19 patients susceptible to nutrient deficiencies and malnutrition. Furthermore, the optimal protein and energy requirements for COVID-19 patients during their ICU stay remain uncertain.

International guidelines recommend energy intakes of 27–30 kcal/kg/day for critically ill patients, using predictive weight-based formulas [9–11]. While indirect calorimetry (IC) has developed over the last years as a preferred method to guide nutritional therapy [9–11], previous studies have relied on predictive equations to establish energy targets [3–5]. Current American and European guidelines for nutritional support in COVID-19 patients suggest protein intake levels of 1.2–1.5 and > 1.3 g protein/kg/day, respectively [9,10,12]. Protein targets are typically calculated using estimated ideal body weight (IBW) formulas, as obesity is highly prevalent in the ICU population [9]. However, these estimations may significantly differ from measured lean body mass (LBM) or fat-free mass (FFM), emerging the need for an objective approach to assess body composition in critically ill patients [13]. Bio-electrical Impedance Analysis (BIA) is a non-invasive method that uses electrodes placed on the hands and feet to pass a low-level electrical current through the body. By measuring the impedance encountered by the current, BIA estimates body composition parameters such as FFM, fat mass, total body water including intra- and extracellular water (ECW). It is a quick and practical assessment tool in clinical settings for evaluating bedside body composition [14]. Our group recently demonstrated variations in LBM among COVID-19 patients with similar actual body weight (ABW), suggesting the importance of calculating protein dosage based on LBM or FFM [13]. Nevertheless, BIA has not yet been widely implemented to determine individual nutrition targets.

This study aims to examine the relationship between energy and protein intake, both based upon ABW and FFM, and 90-day mortality rates in ICU patients with COVID-19. We hypothesized that FFM obtained through individual body composition measures will provide a better reflection of this association compared to ABW.

2. Materials and methods

2.1. Study setting

We conducted a retrospective cohort study at Gelderse Vallei Hospital, Ede, The Netherlands, which is a university-affiliated teaching hospital. The study focused on patients with SARS-CoV-2 infections admitted to our 17-bed mixed medical-surgical ICUs. The study cohort was recruited from the onset of the COVID-19 pandemic on March 18, 2020, until December 1, 2021, when the dominance of the SARS-CoV-2 delta variant waned in the Netherlands. Ethical standards outlined in the Helsinki declaration were followed, and the study received approval from our Institutional Review Board (approval nr: 2202-014).

2.2. Study design and participants

All consecutive ICU patients aged ≥18 years with confirmed SARS-CoV-2 infection by real-time reverse transcriptase polymerase chain reaction (PCR) assay or strong clinical suspicion based on thoracic computed tomographic findings were included. Additional criteria were ICU admission duration of ≥5 days, IMV duration of ≥72 h, and EN as the primary feeding method during ICU stay. Exclusion criteria encompassed transfer from another ICU ≥24 h after IMV initiation, transfer to another ICU within 5 days of IMV initiation, missing 90-day survival data, and participation in any nutritional intervention study.

2.3. Patient management

Starting from August 2020, our ICU implemented a standard treatment protocol for COVID-19 patients, which included dexamethasone 6 mg once daily for ten days and ceftriaxone 2000 mg once daily for four days. From January 25, 2021, a single dose of the interleukin-6 inhibitors tocilizumab (8 mg/kg, maximum of 800 mg) or sarilumab (400 mg) was added to this regimen. EN was provided to all patients receiving IMV through either nasogastric or post-pyloric feeding tubes. Post-pyloric feeding was considered if gastric residual volumes (GRV) exceeded 500 mL and persisted 18 h after the addition of a second prokinetic agent. Additionally, for patients on IMV with a persistent PaO_2/FiO_2 ratio below 150, despite optimizing fluid balance and positive end-expiratory pressure, prone positioning IMV was performed.

2.4. Nutritional assessment and nutrition targets

ABW was measured using beds with built-in scales, while height was measured in bed using a rod. During the first four days of ICU admission, nutrition was increased daily by stepwise increases of 25 %, aiming to reach 100 % of the energy and protein target on day four. Energy targets were calculated according to the formulas recommended by the WHO/FAO/UNU joint expert consultation and the local protocol [15](Table S1). Resting energy expenditure (REE) was determined using IC on the fourth day of ICU admission and every third day thereafter to establish new energy targets. For energy intake adequacy, an energy target reached of 70 % was set as cut-off based on the definition of hypo- and normocaloric intake in accordance with ESPEN guidelines. Protein targets were set at 1.5 g/kg ABW per day, according to the ESPEN and ASPEN guidelines [9,12,16]. To ensure a protein intake within the lower range recommended by ASPEN guidelines (1.2 g/kg/day), the definition for achieving protein goals was set at 80 %. Protein targets based on FFM were set at 1.85 g/kg/day, considering an average FFM of 68 % in hospitalized COVID-19 patients [17,18], with a minimum of 1.2 g/kg/day also falling within the ESPEN guideline range. Patients were categorized based on the percentage of nutritional goals achieved on days 4, 7, and throughout the entire ICU stay, and evaluated using the predefined target cut-offs of 70 % and 80 % for energy and protein intake, respectively.

2.5. BIA measurements

BIA measurements were performed by trained nurses and research staff using the InBody S10® (InBody Co., Ltd., Seoul, Korea). Input parameters included height, weight, and sex. BIA measurements were conducted within 24 h of ICU admission, followed by measurements every third day according to the local protocol. The InBody S10® assessed impedance at multiple frequencies and provided measurements such as whole-body phase angle at 50 kHz, total body water (TBW), ECW, FFM, soft lean mass, percentage body fat, visceral fat area and the ECW/TBW ratio. To account for the impact of fluid overload on soft lean mass and FFM measurements, a correction was applied. FO was calculated by subtracting a recalculated extracellular water based on a standard ECW/TBW ratio of 0.380 from the measured ECW as has been described before [14]. The closest measurement to baseline was used for analysis and FFM-derived nutrition goals calculations.

2.6. Outcomes & data collection

The primary outcome measure was all-cause 90-day mortality, with secondary outcomes including ICU-admission-related complications, GI-related characteristics, ward or ICU mortality, ICU length of stay (ICULOS), hospital length of stay (HLOS), and IMV duration. Patient data, including demographics, comorbidities, nutritional and body composition parameters, clinical scores, laboratory results, COVID-19 associated complications, GI-tolerance related characteristics, and outcome parameters were collected from local electronic medical record systems NeoZis® (MI consultancy, Katwijk, the Netherlands) and MetaVision® (iMDsoft, Tel Aviv, Israel). Dates of death were obtained from the electronic patient record system Xcare® (Nexus, Vianen, the Netherlands), which is connected to the Dutch population register.

2.7. Statistical analysis

In the descriptive analysis, categorical variables were presented as counts and percentages, while continuous variables were reported as mean ± standard deviation (SD) for normally distributed data or median with interquartile ranges [IQR] for non-normally distributed data. Normality of data was assessed using Shapiro–Wilk's test and visual inspection of plots. Group comparisons were performed using Student's T-tests or Mann–Whitney U tests for continuous variables, and Pearson's chi-square test for categorical variables. Proportional hazard-regression models were used to examine the association between energy and protein goals reached and all-cause 90-day mortality, with possible confounders identified using as stepwise approach and the number of covariates matched to the one-to-ten rule. Covariates were excluded in case of multicollinearity (spearman's correlation coefficient >0.7) or when the proportional hazard assumption was violated. Additional subgroup analysis in patients with IC measurements available were performed. Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics 27.0 (IBM Corporation, Armonk, NY, USA; 2020).

3. Results

3.1. Patients

During the study period, a total of 321 COVID-19 patients were admitted to the ICU. Out of these, 85 patients met the inclusion criteria (Fig. 1). The median age of the cohort was 69 years [IQR 63–73], and most patients were male (69.4 %). Among the included patients, 67 (78 %) survived up to 90 days after ICU admission. Comparison of baseline characteristics between survivors and non-survivors are presented in Table 1. There were no significant differences in demographics, comorbidities, laboratory results and clinical scores observed between survivors and non-survivors, except for age (68 years [IQR 61–71] vs 73 years [IQR 67–75], $p = 0.014$). Baseline BIA measurements were available in 72 patients. No significant differences in body composition were found between survivors and non-survivors (Table S2).

3.2. Nutrition intake

Two patients were excluded from the analyses of nutritional intake on days four and seven due to receiving EN for more than 7 day at baseline, and six patients were excluded from the analysis of nutritional intake on day seven as they were discharged from the ICU. Among the 31 (36 %) patients with available REE measurements in the first seven days, median energy targets based on REE measurements and calculations according to the WHO/FAO/UNU did not differ (1649 kcals [IQR 1363–2103] vs 1688 kcals [IQR 1354–1890]; p = 0.451). Additionally, there were no differences between energy targets reached based on REE measurements and calculations on days 4, 7, and throughout the entire ICU stay (58 % [IQR 0.46–0.75] vs 60 % [IQR 0.48–0.82]; $p = 0.569$, and 75 % ± 0.20 vs 79 % ± 0.22; $p = 0.493$, and 77 % ± 0.22 vs 82 % ± 0.19; $p = 0.148$, respectively) in patients of whom REE measurements were available. Therefore, energy goals based the WHO/FAO/UNU formulas were used for the primary analysis in the entire cohort.

Survivors reached a higher median and mean percentage of energy goals during ICU admission based on both ABW and FFM, respectively, compared to non-survivors (87 % [IQR 68–99] vs 62 % [IQR 57–75]; $p = 0.001$ and 104 % ± 27 % vs 73 % ± 18 %; $p < 0.001$, respectively) (Table S3). Additionally, survivors reached a higher percentage of their protein goals based on both ABW and FFM compared to non-survivors during ICU admission (63 % ± 16 % vs 52 % ± 17 %; $p = 0.014$ and 93 % ± 22 % vs 76 % ± 26 %; $p = 0.018$, respectively). Furthermore, no differences in energy and protein intake on days 4 and 7, were observed between survivors and non-survivors.

3.3. Primary outcome

In the primary outcome analysis, reaching ≥70 % of energy goals based on both ABW and FFM during the entire ICU stay was associated with a decreased risk of 90-day mortality (Hazard Ratio (HR) 0.22, 95 % CI 0.08–0.60 and HR 0.28, 95 % CI 0.09–0.85, respectively). Furthermore, reaching ≥80 % of the protein target based on

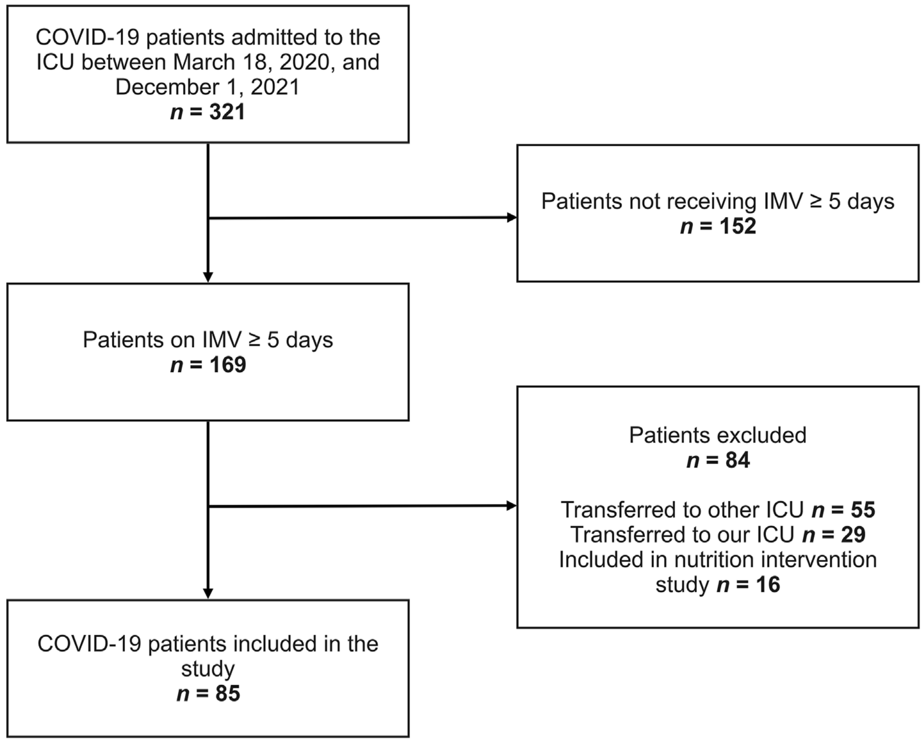

Fig. 1. Flowchart of patient inclusion and exclusion. Abbreviations: COVID-19, Coronavirus Disease 2019; ICU, Intensive Care Unit; IMV, Invasive Mechanical Ventilation.

FFM was also associated with a decreased risk of 90-day mortality (HR 0.26, 95 % CI 0.07–0.94), while no significant association was observed for protein targets based on ABW (HR 0.03, 95 % CI 0.00–3.40). Subgroup analysis in patients of whom REE measurements by IC were available revealed no difference in 90-day survival rates between patients who reached <70 % and ≥70 % of REE-derived energy goal on day 4, 7 and the entire ICU admission (HR 0.69, 95 % CI 0.12–2.91, HR 0.67, 95 % CI 0.17–2.69 and HR 0.65, 95 % CI 0.13–3.22, respectively). Age, which demonstrated the strongest association with 90-day mortality in univariate analysis (Table S4) was included as a covariate in the multivariable analyses. Those who received ≥70 % of the energy goal and ≥80 % of protein target based on FFM had a significantly lower risk of all-cause 90-day mortality compared to patients who received ≥70 % of energy and <80 % of protein goal during ICU admission (adjusted HR 0.12, 95 % CI 0.03–0.50) (Fig. 2; Table S5). However, the analysis based on nutritional goals reached using ABW was not possible due to the survival of all patients who achieved at least 80 % of the protein target based on ABW. There was no observed effect of reaching ≥70 % of energy goals or ≥80 % of protein goals by day 4 or 7 of ICU, both when calculated by FFM and by ABW, on 90-day mortality after correction for age.

3.4. Secondary outcomes

In the present cohort, diarrhoea was the most commonly observed GI-intolerance related characteristic (63.5 %), followed by the need for treatment with prokinetic agents (44.7 %). Prone-positioned ventilation was required for most patients (72.9 %). ICU mortality and hospital mortality rates were 17.6 % and 18.8 %, respectively. Comparison between groups based on the achievement of nutritional goals during ICU stay and secondary outcomes can be found in Supplementary tables S6 A-D. It was observed that patients who reached their nutritional targets based on both ABW and FFM had a longer median duration of IMV, ICULOS, and HLOS. Furthermore, GRV ≥500 mL occurred more often in patients who met their energy and protein goals. Survivors had a longer HLOS compared with non-survivors (25 days [19–39] vs 15 days [12–24], $p = 0.001$), but no differences in ICULOS or IMV duration between survivors and non-survivors were observed, as well as GI-related characteristics during the first seven days after initiation of IMV (Table S7).

4. Discussion

In this single-centre retrospective cohort study including 85 IMV critically ill COVID-19 patients, we found an increased 90-day survival in patients who reached ≥70 % of energy and ≥80 % of protein targets based on FFM during their ICU admission. In addition, receiving ≥70 % of ABW-derived energy goal was also associated with better survival, while ≥80 % of ABW-derived protein goal was not.

Severe COVID-19 cases requiring IMV is associated with poor survival according to a meta-analysis that included studies conducted in the same period as this study, reporting ICU mortality of 43 % [19]. Several therapies, including dexamethasone and interleukin-6 inhibition, have proven their efficacy in improving outcomes of critically ill COVID-19 patients [20]. In the present cohort of critically ill COVID-19 patients, these treatments were not associated with improved survival, while adequate delivery of energy and protein levels throughout ICU admission showed increased survival at day 90. Malnutrition may decelerate rehabilitation and lead to significant muscle loss and impaired physical function, a condition known as ICU-acquired weakness which is associated with increased morbidity and long-term mortality [21]. Our ICU and hospital is highly specialized in providing tailored nutritional therapy which may explain a relatively low mortality rate of 21 %. Moreover, this is in line with COVID-19 ICU survival data from the Dutch National Intensive Care evaluation [22].

Table 1
Baseline characteristics of invasive mechanically ventilated COVID-19 patients included in the study comparing 90 day survivors and non-survivors.

		Total $n = 85$	Survivors $n = 67$	Non-survivors $n = 18$	p-value
Demographics					
Age, years		69 [63–73]	68 [61–71]	73 [67–75]	0.014
Male	n (%)	59 (69.4)	45 (67.2)	14 (77.8)	0.386
Actual Body Weight, kg	Mean (SD)	88.6 (16.5)	89.9 (15.2)	83.8 (20.5)	0.170
BMI, kg/m^2		29.0 [25.6–32.9]	29.5 [25.8–33.5]	27.2 [24.2–30.3]	0.081
Overweight[a] (BMI>25 kg/m^2)	n (%)	36 (42.4)	27 (40.3)	9 (50.0)	0.460
Obese[b] (BMI>30 kg/m^2)	n (%)	35 (41.2)	31 (46.3)	4 (22.2)	0.066
Pre-existing comorbidities	**n (%)**	66 (77.6)	52 (77.6)	14 (77.8)	0.988
Diabetes Mellitus		24 (28.2)	16 (23.9)	8 (44.4)	0.085
Hypertension		32 (37.6)	25 (37.3)	7 (38.9)	0.903
Cardiovascular disease		28 (32.9)	22 (32.8)	6 (33.3)	0.968
NYHA 4		2 (2.4)	2 (3.0)	0	0.458
COPD/Asthma		21 (24.7)	17 (25.4)	4 (22.2)	0.783
Smoker[c]		33 (44.6)	23 (34.3)	10 (62.5)	0.104
Active malignancy		2 (2.4)	2 (3.0)	0	0.458
Renal insufficiency		2 (2.4)	2 (3.0)	0	0.458
Chronic dialysis		1 (1.2)	1 (1.5)	0	0.602
Laboratory Results					
PaO_2/FiO_2[d]		125 [103–163]	129 [103–164]	122 [104–148]	0.490
CRP, mg/L		99 [50–172]	105 [58–174]	70 [34–155]	0.210
Lymphocytes, x10^3/L		0.7 [0.4–1.1]	0.7 [0.4–1.0]	0.9 [0.5–1.3]	0.525
NLR		8.9 [5.1–12.9]	8.9 [4.9–13.1]	9.0 [5.9–12.4]	0.954
Ferritin, μg/L	Mean (SD)	1502 (931)	1546 (879)	1410 (1079)	0.733
Albumin, g/L		27 [25–29]	26 [25–29]	26 [26–30]	0.441
Serum creatinine, μmol/L		75 [60–100]	75 [59–97]	87 [61–112]	0.494
Blood urea nitrogen, mmol/L		7.9 [5.7–10.1]	7.9 [5.3–9.4]	8.6 [6.1–11.1]	0.186
D-dimer, μmol/L		1.8 [0.7–4.7]	1.8 [0.7–4.7]	1.8 [0.7–5.3]	0.982
Clinical scores					
APACHE II		16 [13–19]	16 [13–19]	16 [13–21]	0.884
NUTRIC		4 [3–5]	4 [3–5]	3 [3–5]	0.605
SOFA[e]		7 [6–10]	8 [6–9]	7 [6–10]	0.525
SOFA[f]		7 [6–8]	7 [6–8]	7 [6–8]	0.640
Barthel index		20 [20–20]	20 [20–20]	20 [20–20]	0.265
COVID-19 therapy	**n (%)**				
Dexamethasone		65 (76.5)	53 (79.1)	12 (66.7)	0.269
IL-6 inhibitor		30 (35.3)	26 (38.8)	4 (22.2)	0.191
Dexamethasone and IL-6 inhibitor		30 (35.3)	26 (38.8)	4 (22.2)	0.191
Days until baseline					
From hospital- to ICU admission		1 [0–2]	1 [0–2]	1 [0–2]	0.418
From ICU admission to intubation		1 [1–4]	1 [1–3]	1 [1–4]	0.631

Abbreviations: SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; NYHA, New York heart association; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; APACHE II, acute physiology and chronic health evaluation II; NUTRIC, nutrition risk in critically ill; SOFA, sequential organ failure assessment; IL-6, Interleukin-6.
Data are represented as median [IQR] unless reported otherwise. p-values were calculated using independent sample t-tests, Mann–Whitney U tests, or chi-square tests were appropriate.
[a] BMI 25–30 kg/m^2.
[b] BMI >30 kg/m^2.
[c] Includes active smokers and patients with a history of smoking.
[d] Mean of maximum and minimum PaO_2/FiO_2 ratio at baseline.
[e] At ICU admission.
[f] At baseline.

4.1. Energy intake adequacy

Previous studies that assessed the effect of energy intake on survival of critically ill COVID-19 patients have shown contradictory results. Chada et al. observed that COVID-19 patients who received ≥80 % of recommended energy intake had lower mortality compared to those receiving <80 %, which aligns with our findings [23]. They also found that early energy deficits significantly increased mortality and accumulating nutritional deficits are difficult to correct during the ICU stay. Similarly, Hajimohammadebrahim et al. have shown that nutritional deficits early in ICU stay are linked to increased mortality, with a higher energy intake on day 5 being associated with improved survival [4]. In our study, we observed no difference in mortality between those patients that met their ABW or FFM-derived energy goals, compared to those that did not reach these goals at day 4 or day 7 of ICU stay. This implies that nutritional deficits early in ICU stay may be less harmful to COVID-19 patients, a phase when endogenous energy production is high [24]. However, the study design precludes us of detecting any effects of energy and protein deficits early in the ICU phase on overall mortality rates.

Measuring the REE through IC has been set as the gold standard to assess energy requirements in the ICU. However, in ventilated patients with high respiratory demands a reliable measurement has not been proven possible [24]. Furthermore, in the initial phase of the COVID-19 pandemic, IC was contra-indicated due to risk of contamination. Consequently, REE measurements were only available in 36 % of the COVID-19 patients in the current cohort, which is among the limitations of the study. Subgroup analysis conducted on this subset of IC measured patients revealed no significant impact of reaching REE-derived energy goal of at least 70 % on survival. It is important to acknowledge, however, that the limited sample size of this subgroup may have hampered the ability to reach statistical significance. Furthermore, predictive equations for energy goals may lead to significant errors. Nonetheless, no distinctions between REE and ABW-derived energy goals were

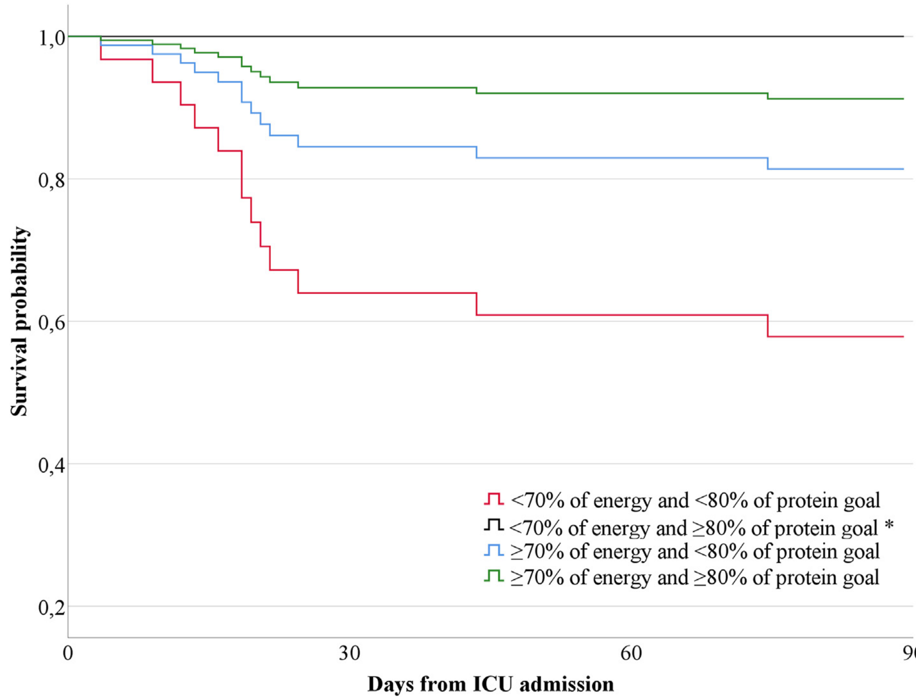

Fig. 2. Cox regression 90-day survival plot of COVID-19 patients divided into groups based on energy and protein goals reached (according to FFM measurements) during ICU-stay. Red <70 % of energy and <80 % of protein goal is reference group red; Blue ≥70 % of energy and <80 % of protein goal adjusted HR 0.37, 95%CI 0.11–1.29); Green ≥70 % of energy and ≥80 % of protein goal (adjusted HR 0.12, 95 % CI 0.03–0.50). Plot and hazard ratios have been corrected for the covariate age. * Only one patient was allocated to the group <70 % of energy and ≥80 % of protein goal reached (black).

observed, suggesting an accurate estimation of energy goals using ABW in the present cohort.

4.2. Protein intake adequacy

Increased protein provision in critically ill patients is vital for maintaining and restoring muscle mass to reduce the risk of comorbidities such as weakness and functional impairment [9]. Although there is no prior research on the effect of BIA-derived FFM for protein provision on mortality of ICU patients, we recently demonstrated that different methods of estimating LBM show poor agreement compared to BIA-derived FFM in critically ill COVID-19 patients [13]. This suggests that protein targets can differ largely from BIA-derived goals when calculated using estimated FFM, thereby risking a protein shortage or surplus. In our patient cohort, in contrast to ABW-derived goals, achieving above the FFM-derived protein goal was associated with lower mortality, highlighting the importance of accurate body composition measurements in calculating individual nutritional needs for critically ill COVID-19 patients. These findings are supported by previous studies showing that protein deficits increase mortality rates in COVID-19 patients [4,5]. Furthermore, comparison of previous studies investigating the efficacy of protein delivery on survival of COVID-19 ICU patients is complicated by the use of different methods to calculate IBW. While several studies have reported reduced mortality when patients received >0.8 g protein/kg IBW/day during ICU stay [5]. While higher protein intake levels on day 5 has been associated with improved survival [4], others reported no effect of an early protein deficit on mortality [3] which aligns with our findings. These contradictory findings undermine the need for further exploration of the effect of protein adequacy on survival rates in COVID-19 patients and may suggest that adequacy of protein targets and clinical outcomes are better evaluated by techniques that are based on body composition such as FFM.

Additionally, we observed no difference in mortality rates when a combination of high energy and low protein intake was administered, indicating the importance of an adequate intake of both energy and protein. Meeting protein goals during hypocaloric feeding has shown minimal harm in previous papers [9]. Surprisingly, patients who achieved the set nutritional targets experienced a longer duration of mechanical ventilation, ICU-, and hospital stay. This suggests that early protein and energy deficiencies may be more commonly compensated for in patients with a longer ICU stay or that improved feeding performance may lead to a longer duration of IMV resulting in a longer ICU stay. Higher energy intake enhances CO_2-production and, therefore, increase the need for ventilation which may delay weaning from mechanical ventilation, as was observed in several clinical trials [25–27].

4.3. Gastro-intestinal intolerance

Other than more frequently observed GRVs≥500 mL in patients who met the set nutritional goals, which is considered an unspecific marker for feeding intolerance in IMV ICU patients [24], no differences in GI-intolerance related characteristics between were found when comparing with those patients who did not meet their goals. In addition, we noticed no differences in GI-intolerance related symptoms between survivors and non-survivors. Previous research has reported a 56 % incidence of feeding intolerance in their COVID-19 cohort [7], higher than the 38 % reported in a previous systematic review of a diverse ICU patient group, and observed that COVID-19 patients with feeding intolerance had increased mortality rates, longer length of ICU stay, and more COVID-19-associated complications [7]. In contrast, Osuna-Padilla et al. found no increased GI intolerance in COVID-19 patients compared to non-COVID-19 patients in the ICU, and no impact of GI intolerance on achieving nutritional goals [18], in line with our findings. Therefore, the presence of GI intolerance in COVID-19 patients may not directly affect mortality. It is possible that a higher incidence of GI intolerance in COVID-19 patients serves as an indicator of disease severity, but further research is needed to establish this relationship.

4.4. Strengths, limitations, and future perspectives

Among the strengths of this study is a high homogeneity in the cohort including severe COVID-19 patients. In addition, this is the first study to investigate the individualised associations between energy and protein intake and 90-day mortality comparing the use of FFM and ABW for nutritional calculations. Nevertheless, the study has a retrospective design and therefore there is a possibility of residual confounding. Future prospective studies should further elucidate this association between achieving energy and protein targets and survival using different body composition measurements in COVID-19 or other viral pneumonia patients in the ICU. Additionally, intervention studies that examine the impact of protein dosing based on FFM measurements on short- and long-term muscle related and functional outcomes during and after ICU stay are a logical progression in this field.

5. Conclusions

This study underscores the significance of providing adequate nutritional therapy to COVID-19 ICU patients who require IMV. Meeting over 80 % of the protein goals based on BIA-derived FFM was associated with lower mortality rates, which emphasizes the need for further investigation into the role of FFM in establishing nutritional targets.

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Conflicts of interest

Prof. Dr. Van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Danone-Nutricia, Rousselot, TNO, AOP Pharma, PAION, Baxter, GE Healthcare, Nestlé and Abbot. The other authors have nothing to declare.

Author contribution

Conceptualization: MM, AJHH, SBH, ARHvZ; Data curation: MM, SBH; Formal analysis: MM, SBH; Writing - Original Draft: MM, AJHH, SBH, ARHvZ; Writing — Review and editing: MM, AJHH, SBH, IWKK; Project administration: MM, AJHH, SBH; Methodology: MM, AJHH, SBH, ARHvZ; Supervision: IWKK, ARHvZ.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.10.002.

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