Early high protein intake and mortality in critically ill ICU patients with low skeletal muscle area and -density

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1. Introduction

Optimal nutritional support for critically ill patients remains a topic of debate. Particularly the optimal dose of protein and energy during the early phase of critical illness is controversial [1]. Several observational studies found associations between (early or overall) high protein intake and improved outcomes [2–8], although these findings have not been confirmed in RCTs [9–13], and even harmful
associations have been found between very early [6,14] or overall [15] protein intake and mortality. Possibly, optimal early nutrition may differ between individual patients and concomitant early energy overfeeding may be harmful. Several studies found benefit of high protein intake only in specific groups of patients (e.g. non-septic, non-overfed patients [2], high nutrition risk in the critically ill (NUTRIC) score patients [4], or patients with normal kidney function [16]), suggesting that identifying specific patients profiting from early high protein intake may be important.

Previous research shows that patients with low skeletal muscle area (SMA) or low skeletal muscle density (SMD) on intensive care unit (ICU) admission have an increased mortality, independent of severity of disease [17–19]. Since muscle comprises the largest protein pool in the body, these patients have lower protein reserves and may therefore benefit from early high protein intake.

The objective of this retrospective database study was to determine whether the quantity of early protein intake is associated with mortality and other clinical outcomes in critically ill patients admitted with normal or low SMA and SMD. We hypothesized that patients with low SMA and low SMD on abdominal computed tomography (CT) scans may benefit from early high protein intake.

2. Subjects and methods

2.1. Patients and data

This retrospective database study evaluated the association between early (day 2–4) protein intake and mortality in three groups of ventilated critically ill patients: normal SMA, low SMA, and a subgroup with combined low SMA and low SMD. Patients were admitted to a medical-surgical ICU of a university hospital (Amsterdam University Medical Centers, location VUMc) from January 2004 to January 2016. All patients admitted during this period were screened for eligibility. Inclusion criteria were age ≥18 years, ICU stay ≥4 days, mechanical ventilation, and an abdominal CT-scan made ≤4 days before or after ICU admission. Patients were excluded if the CT-scan was not suitable for muscle analysis (Appendix 1), data on weight or height were missing, or oral intake was initiated within 4 days.

The study was approved by the VUMc institutional review board (IRB000002991, decision 2012/243). The need for informed consent was waived because of the retrospective nature of the study using coded data obtained from standard care. The study has been registered at ClinicalTrials.gov (NCT02817646).

Patient data including age, sex, weight, height, admission diagnosis, Acute Physiology and Chronic Health Evaluation (APACHE) II score, daily protein and energy intake (including non-nutritional sources), length of ventilation, ICU- and hospital length of stay, discharge destination, and mortality were obtained from the ICU patient data management system (Metavision, IMDsoft, Tel-Aviv, Israel), hospital information system (Mirador, iSOFT Nederland BV, Leiden, The Netherlands), civil registry, or general practitioner.

Primary endpoints were short-term mortality 60 days after ICU admission and long-term mortality 6 months after ICU admission. Secondary endpoints were the odds of being discharged to home, length of ventilation, and ICU- and hospital length of stay.

2.2. CT-scan analysis

Patients were categorized into three groups; admitted with normal SMA, with low SMA, and a subgroup of the low SMA group admitted with combined low SMA and low SMD [18,19].

All abdominal CT-scans made during the study period for diagnostic or interventional purposes ≤4 days before or after ICU admission were reviewed for suitability for muscle analysis. CT-scans were analyzed using Slice-O-matic versions 4.3 and 5.0 (TomoVision, Montreal, QC, Canada) by two certified investigators (WGPM and IMD, trained by the Cross Cancer Institute, Canada). CT-scans were analyzed at the level of the third lumbar vertebra (L3). The precision of single L3 slice CT-scan analysis is high (inter- and intra-observer variability <2%) [20] and L3 SMA is strongly related to whole-body skeletal muscle volume (r = 0.83–0.99, p < .01) [21,22].

Muscle tissue was identified using boundaries in Hounsfield Units (HU) set to <29 to >150 [23]. All muscles present at the L3 level were analyzed. Low SMA was defined using previously found ICU-specific cut-off points: males <170 cm² and females <110 cm², which were associated with hospital mortality. Patients with a low SMA according to these cut-off points had an odds ratio for hospital mortality of 4.3 (95% confidence interval (CI) 2.0–9.0, p < .001) compared to those with normal SMA [18]. The software automatically calculates SMD from the mean radiological attenuation of all L3 muscle. Low SMD was defined using cut-off points the for the 5th percentile from a healthy population of kidney donors (95% of this healthy population had a SMD above these values and 5% below these values): males <29.3 HU and females <22.0 HU [24].

2.3. Protein intake and nutritional protocol

Average daily protein intake over ICU admission day 2–4 was used as early protein intake. Day 1 was excluded to include only full nutrition days. Protein intake was analyzed both as continuous variable and dichotomized using mean day 2–4 intake ≥1.2 g/kg/d or <1.2 g/kg/d.

Enteral nutrition (EN) was initiated within 24 h from ICU admission or after hemodynamic stabilisation. The preferable route was enteral, parenteral nutrition (PN) was provided only when the gut failed, not as supplemental nutrition in the first week.

The protein intake target was 1.2–1.5 g/kg pre-admission body weight per day. Weight was adjusted to weight at body-mass index (BMI) 20 kg/m² for patients with BMI >20 kg/m² and to weight at BMI 27.5 kg/m² for BMI >30 kg/m² [25]. Protein provision was not adjusted in case of renal failure or renal replacement therapy.

Energy target was estimated resting energy expenditure (REE) using the Harris and Benedict 1984 equation [26] +30% for stress and activity.

We previously developed an algorithm to select the best nutritional formula and feeding rate to meet both energy- and protein targets, using several nutritional formulae with a range of energy-to-protein ratios [27].

2.4. Statistical analysis

Independent samples T-tests and Mann–Whitney U-tests were used to compare continuous variables, and Fisher Exact tests and Chi²-tests with post-hoc z-test with Bonferroni correction for categorical variables. Kaplan Meier survival curves were made for the normal SMA, low SMA, and combined low SMA and low SMD groups; and for protein intake (≥1.2 g/kg/d vs. <1.2 g/kg/d) within these groups, with Log-rank tests to compare survival curves.

Cox regression analysis was used to evaluate the association between protein intake (as continuous variable and dichotomous ≥1.2 g/kg/d vs. <1.2 g/kg/d) and 60-day and 6-month mortality, with adjustments for APACHE II score and energy intake as proportion of calculated needs.

To evaluate secondary outcome measures in ICU- or hospital survivors, logistic regression analysis was used for discharge to
home and linear multiple regression analyses for length of ventilation, and ICU- and hospital length of stay. Finally, we performed sensitivity analyses including only patients who were adequately fed (80–120% of energy target); pre-ICU hospital stay of <1 week; excluding trauma patients; with additional adjustments for sex, age, and pre-ICU hospital stay; with cut-off points for skeletal muscle index [28]; and with protein intake expressed in g/kg ideal body weight [29]. Additional information on these statistical analyses can be found in Appendix 2.

IBM SPSS Statistics 22 (IBM Corp, Armonk, NY, USA); R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) with survival-, tidyverse-, and ggfortify packages; and GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA) were used for statistical analysis. Values are reported as mean (±standard deviation, SD) or median [25–75% interquartile range, IQR]. All statistical tests were conducted two-sided. A p < .05 was considered statistically significant.

3. Results

A total of 3,851 patients were admitted to the ICU during the study period for at least 4 days and mechanically ventilated, with a mean APACHE II score of 24.8 (Supplemental Fig. 1). Nine hundred eighty-two patients fulfilled inclusion criteria. After excluding patients with CT-scans not suitable for muscle analysis (n = 210) or missing data (n = 33), 739 patients were available for final analysis.

The CT-scan was made within one day of ICU admission in 595 patients (81%). Of 739 patients, 445 patients (60%) were admitted to the ICU with low SMA, and among these 200 patients (45% of the normal SMA group) with combined low SMA and low SMD. Nutritional and energy intake were not significantly different between muscle groups except that BMI was significantly older, more often male, had a lower weight and BMI, higher APACHE II score, longer pre-ICU hospital stay, and were less often trauma patients when compared to the normal SMA group (Table 1). Early (day 2–4) protein intake was not significantly different between the low- and normal SMA groups (0.70 ± 0.39 vs. 0.75 ± 0.42 g/kg/d, respectively, p = .13). The low SMA group received more energy (90 ± 38% vs. 84 ± 36% of REE, p = .03).

Similar differences were seen between the combined low SMA and low SMD subgroup and the normal SMA group, except that BMI and energy intake were not significantly different (Table 1).

3.3. Mortality in muscle groups

Sixty-day and six-month mortality were 14.6% and 22.1% in the normal SMA group, 32.7% and 42.7% in the low SMA group, and 38.3% and 50.0% in the combined low SMA and low SMD group (all p < .001 vs. normal SMA). Kaplan Meier survival curves of the latter two groups were significantly lower than the normal SMA group (Fig. 1A).

3.4. Protein intake as continuous variable

In adjusted Cox regression analysis with protein intake expressed as continuous variable, no significant association between protein intake and mortality was found in the normal SMA group (Table 3). In the low SMA group, higher early protein intake was associated with lower 60-day mortality (adjusted hazard ratio (HR) per 0.1 g/kg/d 0.82, 95% CI 0.73–0.94) and lower 6-month mortality (HR 0.88, 95%CI 0.80–0.98). Similar associations were found in the combined low SMA and low SMD subgroup (HR 0.76, 95%CI 0.64–0.90 for 60-day mortality and HR 0.80, 95%CI 0.68–0.93 for 6-month mortality). Higher early energy intake was associated with higher 60-day and 6-month mortality in the low SMA group and in the combined low SMA and low SMD subgroup, but not in the normal SMA group. The hazard ratios associated with different levels of protein- and energy intake are visualised in Fig. 2 (60-day mortality) and Supplemental Fig. 2 (6-month mortality).

3.5. Protein intake as dichotomized variable

Kaplan Meier survival curves of patients with an early protein intake ≥1.2 g/kg/d were significantly higher than those who received <1.2 g/kg/d in the combined low SMA and low SMD subgroup (Fig. 1D), but not in the normal- and low SMA groups (Fig. 1B,C).

In the normal SMA group, no significant association was found between protein intake and mortality (Table 3). In the low SMA group, early protein intake ≥1.2 g/kg/d was associated with lower 60-day mortality (HR 0.53, 95%CI 0.29–0.98), and in the combined low SMA and low SMD subgroup with lower 60-day mortality (HR 0.16, 95%CI 0.05–0.55) and lower 6-month mortality (HR 0.32, 95% CI 0.14–0.74).

6. Secondary outcomes

Protein intake was not associated with the odds of discharge to home (Supplemental Table 2). However, higher protein intake as continuous variable was associated with a shorter ICU stay, and both as continuous and dichotomized variable with shorter mechanical ventilation in patients with normal- and low SMA, but not in patients with combined low SMA and low SMD.

3.7. Sensitivity analyses

In sensitivity analyses the results remained robust (Supplemental Table 3).

4. Discussion

This study in mechanically ventilated patients admitted to the ICU for at least four days and having an abdominal CT scan made around admission demonstrates that an early higher protein intake is associated with lower mortality in patients admitted with low skeletal muscle area and -density but not in patients admitted with normal skeletal muscle area when adjusted for confounders energy intake and severity of disease. These findings are relevant because low skeletal muscle area and the combination with low skeletal muscle density on admission are associated with high mortality.

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<table>
<thead>
<tr>
<th>Muscle groups</th>
<th>Normal skeletal muscle area</th>
<th>Low skeletal muscle area</th>
<th>Combined low skeletal muscle area and-density subgroup</th>
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<tbody>
<tr>
<td></td>
<td>Protein &lt; 1.2 g/kg/day</td>
<td>Protein ≥ 1.2 g/kg/day</td>
<td>Protein ≥ 1.2 g/kg/day</td>
</tr>
<tr>
<td></td>
<td>kg/day^2</td>
<td>no.</td>
<td>P-value vs.</td>
</tr>
<tr>
<td></td>
<td>Protein groups</td>
<td>Protein groups</td>
<td>Protein groups</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>52 (36–65) 66 (54–75)</td>
<td>.001</td>
<td>71 (62–77)</td>
</tr>
<tr>
<td>Sex male, No. (%)</td>
<td>179 (61) 304 (68)</td>
<td>.04</td>
<td>144 (72)</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>80 (71–90) 75 (65–82)</td>
<td>.001</td>
<td>79 (70–85)</td>
</tr>
<tr>
<td>BMI, median (IQR), kg/m^2</td>
<td>25.6 (23.5–25.9) 24.4 (22.5–27.8)</td>
<td>&lt;.001</td>
<td>25.1 (23.2–25.7)</td>
</tr>
<tr>
<td>Under-weight, No. (%)</td>
<td>2 (1) 25 (6)</td>
<td>.001</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Normal weight, No. (%)</td>
<td>135 (46) 252 (56)</td>
<td>.001</td>
<td>113 (43)</td>
</tr>
<tr>
<td>Over-weight, No. (%)</td>
<td>122 (41) 129 (29)</td>
<td>.001</td>
<td>111 (43)</td>
</tr>
<tr>
<td>Obese, No. (%)</td>
<td>35 (12) 39 (9)</td>
<td>.001</td>
<td>27 (13)</td>
</tr>
<tr>
<td>APACHE II score, mean (SD)</td>
<td>22 (8) 25 (8)</td>
<td>.001</td>
<td>26 (8)</td>
</tr>
<tr>
<td>Admission category, No. (%)</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
</tr>
<tr>
<td>Medical</td>
<td>95 (32) 224 (50)</td>
<td>.001</td>
<td>117 (58)</td>
</tr>
<tr>
<td>Surgical</td>
<td>199 (68) 221 (50)</td>
<td>.001</td>
<td>83 (42)</td>
</tr>
<tr>
<td>Male</td>
<td>194 (61) 194 (61)</td>
<td>.001</td>
<td>113 (43)</td>
</tr>
<tr>
<td>Female</td>
<td>123 (62) 123 (62)</td>
<td>.001</td>
<td>82 (34)</td>
</tr>
<tr>
<td>Normal skeletal muscle area, median (IQR), cm^2</td>
<td>56 (44–66) 32 (18–46)</td>
<td>.001</td>
<td>52 (37–63)</td>
</tr>
<tr>
<td>Male</td>
<td>59.3 (55.2–64.1) 55.5 (50.1–61.0)</td>
<td>.001</td>
<td>59.3 (55.2–64.1)</td>
</tr>
<tr>
<td>Female</td>
<td>44.5 (40.9–48.7) 34.7 (31.2–43.5)</td>
<td>.001</td>
<td>42.8 (37.0–48.2)</td>
</tr>
<tr>
<td>Time from ICU admission to CT-scan, mean (SD), d</td>
<td>0 (0) 0 (0)</td>
<td>.001</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Length of pre-ICU hospital stay, median (IQR), d</td>
<td>0 (0–1) 1 (0–4)</td>
<td>.001</td>
<td>0 (0–1)</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of patients with mean day 2–4 protein intake <1.2 g/kg/day or ≥1.2 g/kg/day in patients admitted with low skeletal muscle area or combined low skeletal muscle area and-density.
and appear to be common among critically ill patients (60% and 27% respectively). This study suggests that these patients may benefit from an early protein intake of ≥1.2 g/kg/d. Although our findings have a physiological rationale and were robust in sensitivity analyses, no inferences about causality can be made in this retrospective study and randomized studies are needed to exclude residual confounding and assess causality. Nevertheless, this is the largest study up to now combining both muscle- and nutritional data and our findings may be a first step to personalized nutritional support during critical illness.

4.1. High protein intake

We previously found an association between day 4 protein intake of ≥1.2 g/kg/d and lower hospital mortality in non-septic, non-overfed, and critically ill patients [2]. In the current study, we identify a subgroup which may specifically benefit from early high protein intake.

A association between higher protein intake and lower mortality was demonstrated in several observational studies in a heterogeneous ICU population [3,5,7]. Few studies specifically report early protein intake. In a prospective cohort study, Bendavid et al. found an association between a protein intake of >0.7 g/kg/d during the first 3 days of ICU admission and lower 60-day all-cause mortality [8]. Additionally, in another large retrospective cohort study, Zusman et al. also found a significant association between day 3 protein intake of 1 g/kg/d and lower mortality [30]. However, higher protein delivery in the first week was found to be associated with greater muscle wasting in a small selected cohort of patients with prolonged critical illness [15]. Additionally, Koekkoek et al. found lower mortality when protein intake was gradually increased during 7 days [6]. Similarly, a post-hoc analysis of the EPaNIC trial suggested that the day 3 protein/amino acid dose, rather than the glucose dose, explained the delayed recovery in the early PN group [14]. However, on day 5 and day 7 this association was not found. Thus, especially the optimal protein dose early during critical illness is still controversial.

These seemingly contrasting findings suggest that optimal nutritional strategies may differ between patients. Certain subgroups may benefit while others may not. Indeed, in a post-hoc subgroup analysis of the Nephro-protective randomized trial, reduced mortality was observed only in patients with normal kidney function allocated to receive high protein [16]. Additionally, an association between greater protein adequacy and lower mortality was found only in patients with a high NUTRIC score [4]. The present study suggests that specifically patients with low SMA and low SMD may benefit from early high protein intake.

The contrasting findings regarding early protein intake may also be attributed to concomitant energy overfeeding. Because of inflammation-induced endogenous energy production, hypocaloric nutrition is recommended during early critical illness [2,3,31]. In the well-designed EAT-ICU trial, early goal directed nutrition was not associated with improved outcomes [12]. Furthermore, the INTACT trial was stopped prematurely because of higher mortality in the intensive medical nutrition therapy group [13]. In both trials, the high-protein groups received full energy from day 1 with inherent risk of early energy overfeeding. In the current study, mean energy intake was frequently at or above target as well and the high-protein groups received full energy from day 1 with inherent risk of early energy overfeeding.
randomized study avoiding energy overfeeding by the use of protein supplements or a high protein-to-energy ratio nutrition.

4.2. Low skeletal muscle density and protein intake

In the present study, the association between high protein intake and lower mortality was more pronounced in patients admitted with combined low SMA and SMD. While a low SMA is an indication of low muscle mass and therefore low protein reserves, low SMD is associated with qualitative changes in muscle such as fatty infiltration or myosteatosis [32]. Myosteatosis may create an environment with low-grade inflammation and insulin resistance [33–35], which contribute to anabolic resistance [36]. A higher protein intake may be needed to overcome this anabolic resistance. This may additionally explain why the most apparent benefit of protein intake was seen in the patients with combined low SMA (low reserves) and low SMD (anabolic resistance). However, these explanations remain speculation.

4.3. Low skeletal muscle area and -density

The high prevalence of both low SMA and low SMD found in this study, as well as the increased mortality in these groups, are in line with other studies [17–19,37,38]. Identifying these patients may improve risk-stratification and help guide treatments. However, accurately doing so remains a challenge. BMI or other simple anthropometric measurements are not accurate, because they do not detect sarcopenic obesity [39]. Although CT-scanning may provide accurate measurements of muscle area and density, routine CT-scanning is not feasible in critically ill patients due to costs, time, risks associated with transport, and exposure to radiation. However, some of these limitations may be offset and automatic CT-scans analysis for determining SMA and SMD may become clinically available when novel artificial intelligence-based methods are integrated into routine image analysis [40,41]. Additionally, alternative bedside methods to measure body composition in the ICU are available, although each has its own limitations [42]. Musculoskeletal ultrasound provides both muscle mass and quality, although standardized protocols and cut-off points are lacking. For bio-electrical impedance analysis these are available, however, concerns exist about the applicability of algorithms to calculate muscle mass in critically ill patients.

4.4. Strengths and limitations

The high accuracy of CT-scan analysis to measure SMA and SMD adds to the validity of our findings. Furthermore, the use of an algorithm to select the optimal nutrition from several nutritional formulae with a range of energy-to-protein ratios, rather than using one nutritional formula with a fixed energy-to-protein ratio, provided enough statistical variation to analyze protein intake and energy intake separately.

We also acknowledge several limitations to this study. It is a retrospective study and therefore no inferences about causality can be made: our results are hypothesis-generating only. Possibly, the association between high protein intake and lower mortality is confounded by less severely ill patients reaching higher protein intakes. However, we corrected for severity of illness and the results were robust in a sensitivity analysis including only patients who were adequately fed. Additionally, baseline differences...
Cox regression analyses on the association between mean day 2–4 protein intake <1.2 g/kg/day or ≥1.2 g/kg/day within muscle groups.

Table 2

| Normal skeletal muscle area<br>P-value | Protein intake <1.2 g/kg/day<br>n = 260 | Protein intake ≥1.2 g/kg/day<br>n = 34 | 60-day mortality, No. (%)<br>.44 | 122 (34) | 17 (25) | .16 | 72 (43) | 3 (11) | .001 |
|----------------------------------------|------------------------------------------|------------------------------------------|---------------------------------|----------------|---------|------|----------------|---------|------|------|
| Low skeletal muscle area<br>P-value | Protein intake <1.2 g/kg/day<br>n = 372 | Protein intake ≥1.2 g/kg/day<br>n = 73 | 6-month mortality, No. (%)<br>.64 | 154 (44) | 26 (38) | .50 | 90 (54) | 8 (29) | .02 |

Length of ventilations, median (IQR), d

| Length of ICU stay, median (IQR), d | Length of hospital stay, median (IQR), d | Destination after discharge, No. (%)<br>.85 | .10 | .49 |
|------------------------------------|------------------------------------------|------------------------------------------|------|------|------|
| Home<br>87 (38) | 13 (43) | 80 (33) | 25 (45) | 33 (35) | 11 (44) |
| Other hospital<br>40 (22) | 4 (13) | 68 (28) | 11 (19) | 25 (28) | 4 (16) |
| Nursing home<br>42 (18) | 6 (20) | 53 (21) | 14 (25) | 27 (29) | 7 (28) |
| Rehabilitation unit<br>31 (14) | 5 (17) | 25 (10) | 6 (11) | 5 (5) | 3 (12) |
| Other<br>19 (8) | 2 (7) | 20 (8) | 0 (0) | 3 (3) | 0 (0) |

ICU: intensive care unit.

P-values in bold indicate a significant test result.

a. Skeletal muscle area cut-offs: 170 cm² for males and 110 cm² for females, [15] skeletal muscle density cut-offs: 29.3 HU for males and 22.0 HU for females [21].
b. Mean protein intake on day 2–4.
c. Due to losses to follow-up, standardized mortality was known for a subset of patients. Sixty-day mortality n = 699. Six-month mortality n = 690.
d. Length of ventilation and length of ICU stay in ICU survivors only, n = 619.

Table 3

Cox regression analyses on the association between mean day 2–4 protein intake and 60-day- and 6-month mortality.

<table>
<thead>
<tr>
<th>Protein intake - continuous&lt;br&gt;P-value</th>
<th>60-day mortality</th>
<th>6-month mortality</th>
<th>Protein intake - dichotomized&lt;br&gt;P-value</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein intake&lt;br&gt;HR 95%CI</td>
<td>HR 95%CI</td>
<td>HR 95%CI</td>
<td>Protein intake&lt;br&gt;HR 95%CI</td>
<td>HR 95%CI</td>
<td>HR 95%CI</td>
<td>HR 95%CI</td>
<td>HR 95%CI</td>
</tr>
<tr>
<td>Normal SMA&lt;br&gt;Protein intake&lt;br&gt;0.91</td>
<td>0.79–1.05</td>
<td>0.92</td>
<td>0.72–1.18</td>
<td>0.57</td>
<td>0.18–1.86</td>
<td>0.28</td>
<td>0.07–1.08</td>
</tr>
<tr>
<td>APACHE II score&lt;br&gt;1.07</td>
<td>1.03–1.12</td>
<td>1.06</td>
<td>1.04–1.08</td>
<td>1.06</td>
<td>1.04–1.08</td>
<td>1.06</td>
<td>1.04–1.08</td>
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<tr>
<td>Energy intake&lt;br&gt;0.92</td>
<td>0.09–9.33</td>
<td>0.82</td>
<td>0.73–0.94</td>
<td>0.66</td>
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<td>0.29–0.98</td>
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<tr>
<td>Low SMA&lt;br&gt;Protein intake&lt;br&gt;0.92</td>
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<td>0.82</td>
<td>0.73–0.94</td>
<td>0.66</td>
<td>0.40–1.09</td>
<td>0.53</td>
<td>0.29–0.98</td>
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<td>1.06</td>
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<td>Energy intake&lt;br&gt;3.93</td>
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<td>0.64–0.90</td>
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<td>1.02–1.08</td>
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</tr>
<tr>
<td>Energy intake&lt;br&gt;13.65</td>
<td>2.39–77.95</td>
<td>1.98</td>
<td>0.90–4.37</td>
<td>1.98</td>
<td>0.90–4.37</td>
<td>1.98</td>
<td>0.90–4.37</td>
</tr>
</tbody>
</table>

APACHE: acute physiologic, age, and chronic health evaluation, HR: hazard ratio, SMA: skeletal muscle area, SMD: skeletal muscle density.

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between the protein intake groups exist. For example, patients with an early high protein intake had a significantly lower body weight. To account for these baseline differences we performed sensitivity analyses including all significantly different baseline variables, and recalculated protein intake into g/kg ideal body weight. Results were robust in these analyses. Additionally, while higher protein intake was associated with lower mortality, higher energy intake was associated with higher mortality, supporting a specific role of protein and not volume of nutrition. Nevertheless, residual confounding is possible. Furthermore, we included only patients in whom an early abdominal CT-scan was available. This selection bias limits the generalizability of our findings. Finally, we used ICU- and sex-specific cut-off points for SMA which have not yet been validated elsewhere and are not normalized to height [18]. However, in sensitivity analysis using commonly used cut-off points for oncology patients by Martin et al. which are normalized to height [28], we found similar results.

In this retrospective database study in mechanically ventilated critically ill patients, an early high protein intake, particularly of more than 1.2 g/kg/d, was associated with lower mortality in patients admitted with low skeletal muscle area and -density, but not in those with normal muscle area. Further studies are needed to evaluate these findings in a prospective randomized design.

Author contributions

WL, AB, and PW designed research; WL, ID, HO, and PW conducted research; AG provided essential materials; WL and PW analyzed data and performed statistical analysis; WL, HO, and PW wrote the paper; WL had primary responsibility for final content. All authors read and approved the final manuscript.

Conflicts of interest

WL has received congress support and speaker’s honorary from Baxter and Fresenius-Kabi.
AG holds stock options as commissioner of a start-up company for development of new antibiotics.
HO has received congress support and speaker’s honorary from Abbott, Baxter/Gambro, Fresenius-Kabi, Nestlé and Nutricia.
PW has received funds from Baxter, Fresenius-Kabi, Nestlé, and Nutricia.
ID and AB have no conflicts of interest.

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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.2019.09.007.

References


