Early high protein provision and mortality in ICU patients including those receiving continuous renal replacement therapy

Author(s)
van Ruijven, Isabel M. ; Stapel, Sandra N. ; Girbes, Armand R. J. ; Weijs, Peter J. M.

DOI
10.1038/s41430-022-01103-8

Publication date
2022

Document Version
Author accepted manuscript (AAM)

Published in
European Journal of Clinical Nutrition

European Journal of Clinical Nutrition www.nature.com/ejcn

ARTICLE

Check for updates

Nutrition in acute and chronic diseases

Early high protein provision and mortality in ICU patients including those receiving continuous renal replacement therapy

Isabel M. van Ruijven [1,2,3,4], Sandra N. Stapel [1], Armand R. J. Girbes [1] and Peter J. M. Weijs [1,2,3] ✉

BACKGROUND: Findings on the association between early high protein provision and mortality in ICU patients are inconsistent. The relation between early high protein provision and mortality in patients receiving CRRT remains unclear. The aim was to study the association between early high protein provision and hospital and ICU mortality and consistency in subgroups.
METHODS: A retrospective cohort study was conducted in 2618 ICU patients with a feeding tube and mechanically ventilated ≥48 h (2003–2016). The association between early high protein provision (≥1.2 g/kg/day at day 4 vs. <1.2 g/kg/day) and hospital and ICU mortality was assessed for the total group, for patients receiving CRRT, and for non-septic and septic patients, by Cox proportional hazards analysis. Adjustments were made for APACHE II score, energy feeding, BMI, and age.
RESULTS: Mean protein provision at day 4 was 0.98 ± 0.48 g/kg/day. A significant association between early high protein and lower hospital mortality was found in the total group (HR 0.48, 95% CI 0.39–0.60, $p = <0.001$), CRRT-receiving patients (HR 0.62, 95% CI 0.39–0.99, $p = 0.045$) and non-septic patients (HR 0.56, 95% CI 0.44–0.71, $p = <0.001$). However, no association was found in septic patients (HR 0.71, 95% CI 0.39–1.29, $p = 0.264$). These associations were very similar for ICU mortality. In a sensitivity analysis for patients receiving a relative energy provision >50%, results remained robust in all groups except for patients receiving CRRT.
CONCLUSIONS: Early high protein provision is associated with lower hospital and ICU mortality in ICU patients, including CRRT-receiving patients. There was no association for septic patients.

European Journal of Clinical Nutrition; https://doi.org/10.1038/s41430-022-01103-8

BACKGROUND

ICU patients experience a severe loss of muscle mass occurring early and rapidly during the first week of critical illness [1]. Furthermore, a low skeletal muscle mass on ICU admission is a risk factor for mortality in ICU patients [2, 3]. The aim of protein provision is to minimize muscle (protein) losses. Early high protein provision has been shown to be associated with lower mortality in ICU patients [4–7]. Current protein recommendations for ICU patients range from 1.2 to 2.0 g/kg per day [8, 9]. However, the optimal timing of this high protein provision remains unclear. In a prospective observational study, Weijs et al. found that early (day 4) protein provision of at least 1.2 g/kg/day was associated with lower mortality in non-septic, non-energy overfed mechanically ventilated patients [4]. The prospective cohort study by Allingstrup et al. showed early high protein to be associated with lower mortality as well [5]. In line with these findings, Bendavid et al. retrospectively found very early (day 1 to 3) protein provision of more than 0.7 g/kg/day to be associated with lower mortality [6]. However, Koekoek et al. found an association between protein provision of more than 0.8 g/kg/day before day 3 and increased mortality. Only after day 3, they found intermediate protein (0.8–1.2 g/kg/day) to be associated with lower mortality [7].

As a result of increased protein losses, ICU patients receiving continuous renal replacement therapy (CRRT) might benefit from an even higher protein provision [10]. The current ASPEN guidelines recommend a protein provision up to 2.5 g/kg per day for patients receiving CRRT [9]. This recommendation is based on reported amino acid (AA) losses during CRRT and on studies investigating the relation between protein intake and nitrogen balance and AA profile [11, 12]. However, a neutral nitrogen balance is a surrogate endpoint and does not necessarily reflect improved outcome. The relation between early high protein provision and mortality in patients receiving CRRT remains unclear.

Other studies suggested that early high protein provision in ICU patients inhibits autophagy, which might be detrimental for recovery of the ICU patient [13]. In septic patients, autophagy plays an important role in multiple organs, which may reduce

[1]Department of Adult Intensive Care Medicine, Amsterdam University Medical Centers, VU University, Amsterdam, The Netherlands. [2]Department of Nutrition and Dietetics, Amsterdam University Medical Centers, VU University, Amsterdam, The Netherlands. [3]Faculty of Sports and Nutrition, Center of Expertise Urban Vitality, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands. [4]Department of Internal Medicine, Division of Dietetics, Erasmus University Medical Center, Rotterdam, The Netherlands. ✉email: p.weijs@amsterdamumc.nl

Received: 16 April 2021 Revised: 7 February 2022 Accepted: 9 February 2022

benefit of early high protein provision [14]. Lower protein doses have been demonstrated to be beneficial in septic patients [15].

We hypothesized that early high protein provision is associated with lower mortality in ICU patients, including patients receiving CRRT. The aim of the study was to investigate the association between early (day 4) high protein provision and hospital and ICU mortality in ICU patients and consistency in subgroups: patients receiving CRRT, non-septic patients, and septic patients.

METHODS

A retrospective cohort study was conducted based on a new database: the AmsterdamUMCdb version 1.0.2, supported by the European Society of Intensive Care Medicine. This database contains prospectively registered data on all ICU admissions at the Amsterdam University Medical Centers, location VUmc in the period 2003 to 2016 [16].

Inclusion criteria were: mechanical ventilation ≥48 h in the first 4 days of admission, presence of a feeding tube in the first 4 days, data on nutrition in the first 4 days and data on weight and height. Readmissions were excluded from analysis. Analyzed subgroups were patients receiving CRRT, non-septic and septic patients. Patients were assigned to the CRRT subgroup if they were treated with CRRT for at least 24 h within the first 4 days of admission.

Information on age, height, weight at admission (preferably measured, but estimated if not available), readmission, presence of sepsis on admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score, mechanical ventilation, nutritional intake, CRRT and the presence of a feeding tube, hospital mortality and ICU mortality, were derived from the database. Both energy and protein from enteral and parenteral nutrition, propofol, and glucose infusions were taken into account. Relative energy provision was defined as the average energy provision over day 2 to 4 relative to resting energy expenditure. Energy expenditure was predicted by using the Harris and Benedict (1984) equation [17] with additions of 20% for stress and 10% for activity [17, 18]. Relative energy provision was categorized in groups receiving <80%, 80–110%, and ≥110% of Harris and Benedict +30%. Early high protein provision was defined as a protein provision at day 4 of ≥1.2 g/kg/day versus <1.2 g/kg/day.

Statistical analysis

Q5 Data were analyzed by using IBM SPSS Statistics for Mac, version 26.0 (IBM Corp., Armonk, NY, USA). Mean and standard deviations, median and 25th to 75th percentiles or percentages were noted depending on appropriateness. Differences between patients with protein provision of ≥1.2 versus <1.2 g/kg/day were tested (two-sided) for the total study population and for subgroups. In case of normally distributed continuous variables, differences were tested by performing a independent samples t-test. The Mann–Whitney *U* test was performed in case of non-normally distributed continuous variables. Fisher's exact or Chi-square test was performed in testing dichotomous- or categorical variables. Furthermore, Kaplan–Meier survival curves were constructed including the corresponding Log-rank test *p* value. Cox proportional hazards analysis was conducted to assess the association between early (day 4) protein provision (≥1.2 versus <1.2 g/kg) and hospital and ICU mortality. Adjustments for APACHE II score, relative energy provision (categorized as <80%, 80–110%, and ≥110% of calculated need as Harris & Benedict +30%), Body Mass Index (BMI) (categorized as <25, 25–30, and ≥30 kg/m^2) and age group (categorized as 18–39, 40–49, 50–59, 60–69, 70–79, and 80+ years) were made. A sensitivity analysis was performed in patients receiving >50% of relative energy provision. This indicates that patients were fed reasonably well and that protein provision was not dependent on severity of illness, as more severely ill patients may not tolerate (adequate) nutrition. Statistical significance was set at $p = <0.05$.

RESULTS

A total of 23,106 admissions were registered in the database of which 2997 readmissions were excluded. Data on sepsis on admission was missing in 1352 patients. These patients were included in the total group and CRRT-receiving group, but not in the septic and non-septic groups. Subgroups that were created existed of patients receiving CRRT ($n = 350$), non-septic patients ($n = 1073$) and septic patients ($n = 193$). The inclusion of patients is presented in Fig. 1.

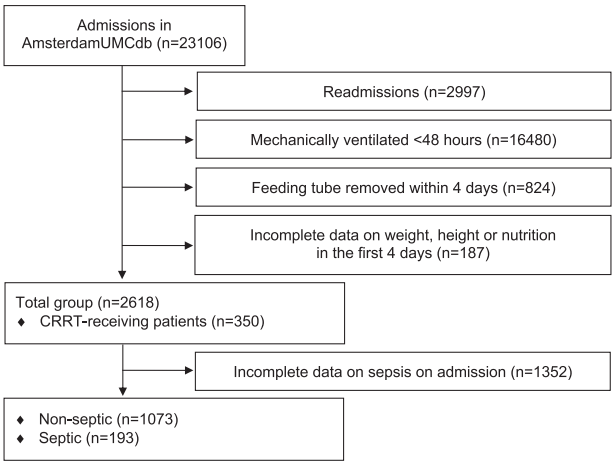

Fig. 1 Flowchart presenting inclusion of patients and analyzed subgroups. Q6

Characteristics of the total group overall as well as subdivided by protein provision ≥1.2 g/kg/day and <1.2 g/kg/day are presented in Table 1. The total group comprised 65.7% male patients. Protein provision at day 4 was 0.98 ± 0.48 g/kg/day. Median hospital stay was 23.7 days (25th to 75th percentile 11.1 to 42.4), hospital mortality was 32.0%. Median ICU stay was 10.5 days (25th to 75th percentile 6.1 to 19.7), ICU mortality was 25.8%.

Characteristics of the subgroups are presented in Supplementary Table 1. Length of hospital and ICU stay and length of mechanical ventilation were significantly higher in patients receiving ≥1.2 g/kg/day in all groups. Weight and BMI were lower in the group receiving ≥1.2 g/kg/day. Age was significantly higher in the non-septic group receiving ≥1.2 g/kg/day. Q7 Q8

Hospital mortality rates were significantly lower in patients receiving ≥1.2 g/kg/day in the total group (27.0% vs. 36.0%, $p = <0.001$), CRRT-receiving patients (45.8% vs. 59.5%, $p = 0.017$) and non-septic patients (31.3% vs. 43.4%, $p = <0.001$) but not in septic patients (34.4% vs. 38.0%, $p = 0.654$). At 60 days, differences between mortality rates were similar in all groups except for CRRT-receiving patients, in whom significance was lost (39.8% vs. 49.6%, $p = 0.090$). Mortality rates are presented in Table 1, Supplementary Table 1, and Supplementary Fig. 1.

Kaplan–Meier survival curves showed lower mortality at 6 months in patients receiving ≥1.2 g/kg/day in the total group ($p = <0.001$), CRRT-receiving patients ($p = 0.008$), non-septic patients ($p = <0.001$), and septic patients ($p = 0.427$). At 60 days, Kaplan–Meier survival curves showed a similar association for all groups except for septic patients ($p = 0.323$). Corresponding Kaplan–Meier curves are presented in Supplementary Fig. 2.

Unadjusted and adjusted analyses are presented in Table 2. The full adjusted model including APACHE II score, relative energy provision, BMI and age is presented in Supplementary Table 2A, B. Adjusted HR's are presented in Fig. 2.

Unadjusted analysis showed a significant association between protein provision and 6-month mortality in all groups, except for septic patients. Adjusted analysis showed a significant association with 6-month mortality in the total group (HR 0.65, 95% CI 0.56–0.74, $p = <0.001$), CRRT-receiving patients (HR 0.62, 95% CI 0.44–0.86, $p = 0.005$) and non-septic patients (HR 0.54, 95% CI 0.44–0.66, $p = <0.001$). No association was found in septic patients (HR 0.76, 95% CI 0.45–1.28, $p = 0.301$). Similar associations were found for 60-day mortality.

In a sensitivity analysis in patients receiving >50% of their estimated energy requirement results remained robust for all groups, except for CRRT-receiving patients ($n = 229$, hospital mortality HR 0.79, 95% CI 0.53–1.18, $p = 0.251$; ICU mortality HR

Table 1. Characteristics of the study population ($n = 2618$).

Variables	Total group ($n = 2618$)	≥1.2 g/kg/day ($n = 1161$)	<1.2 g/kg/day ($n = 1457$)	*p* value*
Sex (male) [*n* (%)]	1720 (65.7%)	747 (64.3%)	973 (66.8%)	0.199[F]
Admission diagnosis sepsis [*n* (%)] ($n = 1266$)	193 (15.2%)	93 (15.7%)	100 (14.8%)	0.695[F]
Hospital mortality [*n* (%)]	837 (32.0%)	313 (27.0%)	524 (36.0%)	**<0.001**[F]
ICU mortality [*n* (%)]	676 (25.8%)	234 (20.2%)	442 (30.3%)	**<0.001**[F]
Length of hospital stay (days) [Mdn (25th to 75th percentile)]	23.7 (11.1 to 42.4)	26.5 (14.1 to 44.8)	20.6 (9.0 to 39.2)	**<0.001**[M]
Length of ICU stay (days) [Mdn (25th to 75th percentile)]	10.5 (6.1 to 19.7)	12.0 (7.5 to 21.1)	9.1 (4.9 to 18.3)	**<0.001**[M]
Ventilation duration (days) [Mdn (25th to 75th percentile)]	7.8 (4.4 to 14.5)	8.7 (5.5 to 15.0)	7.0 (3.7 to 13.7)	**<0.001**[M]
CRRT duration (days) in CRRT-receiving patients ($n = 350$) [Mdn (25th to 75th percentile)]	5.6 (3.1 to 9.8)	5.6 (3.4 to 10.0)	5.6 (3.0 to 9.6)	0.231[M]
Weight (kg) [Mdn (25th to 75th percentile)]	75.0 (65.0 to 85.0)	72.0 (65.0 to 80.0)	80.0 (70.0 to 90.0)	**<0.001**[M]
Height (cm) [M ± SD]	175 ± 10	175 ± 10	175 ± 10	0.106[T]
APACHE II score [M ± SD]	23.6 ± 7.0	23.4 ± 6.8	23.7 ± 7.2	0.222[T]
Mean energy provision at day 2–4 (kcal/day) [M ± SD]	1420 ± 589	1733 ± 442	1170 ± 572	**<0.001**[T]
Relative energy provision at day 2–4 (%) [M ± SD][a]	71 ± 29	89 ± 21	56 ± 26	**<0.001**[T]
Protein provision at day 4 (g/day) [M ± SD]	72 ± 37	99 ± 18	51 ± 34	**<0.001**[T]
Protein provision at day 4 (g/kg/day) [M ± SD]	0.96 ± 0.48	1.38 ± 0.15	0.63 ± 0.40	**<0.001**[T]
BMI (kg/m^2) [*n* (%)]				
<25	1564 (59.7%)	775 (66.8%)	789 (54.2%)	**<0.001**[F]
25–30	764 (29.2%)	347 (29.9%)	417 (28.6%)	
≥30	290 (11.1%)	39 (3.4%)	251 (17.2%)	
Age group [*n* (%)]				
18–39 years	327 (12.5%)	124 (10.7%)	203 13.9%)	0.111[C]
40–49 years	294 (11.2%)	134 (11.5%)	160 (11.0%)	
50–59 years	470 (18.0%)	203 (17.5%)	267 (18.3%)	
60-69 years	618 (23.6%)	284 (24.5%)	334 (22.9%)	
70–79 years	614 (23.5%)	290 (25.0%)	324 (22.2%)	
80+ years	295 (11.3%)	126 (10.9%)	169 (11.6%)	
Category [*n* (%)] ($n = 914$)				
Medical	620 (67.8%)	284 (68.1%)	336 (67.6%)	0.887[F]
Surgical	294 (32.2%)	133 (31.9%)	161 (32.4%)	

Independent samples t—(T), Mann–Whitney *U* (M), Fisher's Exact (F), and Chi-square (C) tests were performed.
APACHE acute physiology and chronic health evaluation, *BMI* body mass index, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit, *M* mean, *Mdn* median, *SD* standard deviation.
[a]Average energy provision over day 2 to 4 relative to resting energy expenditure (REE) predicted by using the Harris and Benedict (1984) equation + 30%.

0.78, 95% CI 0.50–1.22, $p = 0.276$). Sensitivity analysis are presented in Supplementary Table 2C, D.

DISCUSSION

In this study we showed that early high protein provision was significantly associated with lower hospital and ICU mortality in the total group, CRRT-receiving patients, and non-septic patients, however not in septic patients. Our findings support current ESPEN and ASPEN guidelines to provide at least 1.2 g/kg/day protein in most ICU patients including CRRT-receiving patients, but excluding septic patients [8, 9]. Guidelines provide little advice on timing of protein provision. While most discussion is on early feeding, we show that early high protein feeding appears beneficial for patient outcome.

It is worth noting that in all groups, patients with higher protein provision, had a higher length of hospital stay, ICU stay and length of mechanical ventilation. This is in line with the study by Singer et al. [19]. Other studies have shown a decrease in mechanical ventilation days in patients receiving low-carbohydrate nutrition [20, 21]. In the current study, patients with higher protein provision also received higher energy provision. The underlying rationale suggests that by providing more energy, metabolic load and thus carbon dioxide increases, leading to prolonged mechanical ventilation and longer ICU stay as result.

Our findings in the total ICU group are in line with previous studies that found early high protein provision to be associated with lower mortality [5, 6]. Nevertheless, contrary findings were reported by Koekkoek et al. showing that high protein provision ≥1.2 g/kg/day at day 3 to 5 was associated with higher 6-month mortality compared to 0.8–1.2 g/kg/day [7]. It should be noted that this study did not exclude septic patients. Moreover, it is not clear whether these analyses were adjusted for relative energy provision. As suggested by the results of Looijaard et al. early energy overfeeding might be counterproductive to the beneficial effect of early high protein provision due to endogenous glucose production [22].

More specifically, for CRRT-receiving patients early high protein provision was also found to be associated with lower hospital mortality. The association for ICU mortality was also significant.

Table 2. Unadjusted and adjusted cox regression analysis for patients receiving ≥1.2 g/kg/day versus <1.2 g/kg/day protein at day 4 and hospital and ICU mortality.

	Unadjusted			Adjusted[a]		
	HR	95% CI	*p* value**	HR	95% CI	*p* value**
Total group ($n = 2618$)						
Hospital mortality	0.63	0.55–0.73	**<0.001**	0.48	0.39–0.60	**<0.001**
ICU mortality	0.55	0.47–0.64	**<0.001**	0.49	0.39–0.62	**<0.001**
CRRT-receiving ($n = 350$)						
Hospital mortality	0.67	0.49–0.94	**0.045**	0.62	0.39–0.99	**0.045**
ICU mortality	0.59	0.47–0.64	**<0.001**	0.59	0.36–0.97	**0.036**
Non-septic ($n = 1073$)						
Hospital mortality	0.53	0.43–0.66	**<0.001**	0.56	0.44–0.71	**<0.001**
ICU mortality	0.41	0.32–0.53	**<0.001**	0.51	0.39–0.67	**<0.001**
Septic ($n = 193$)						
Hospital mortality	0.68	0.40–1.15	0.148	0.71	0.39–1.29	0.264
ICU mortality	0.53	0.29–0.96	**0.037**	0.61	0.30–1.22	0.157

[a]Adjusted for APACHE II score, relative energy provision, BMI, and age.
**Bold *p* values represent statistical significance $p = <0.05$.

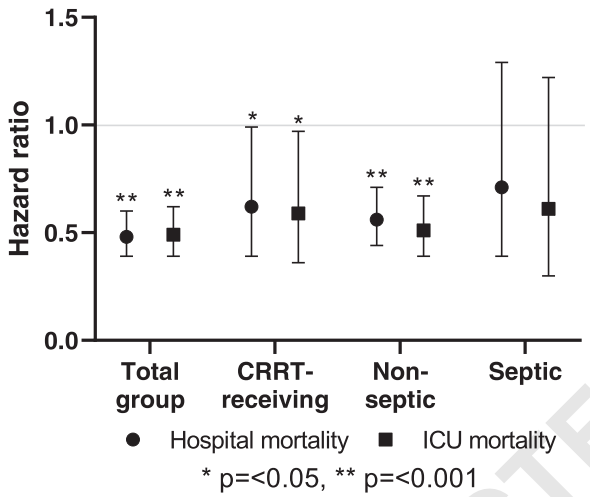

Fig. 2 Hazard ratios for hospital and ICU mortality in patients receiving ≥1.2 g/kg/day versus <1.2 g/kg/day protein at day 4, adjusted for APACHE II score, relative energy provision, BMI, and age group.

Our finding of lower mortality in CRRT-patients receiving early high protein, is in contrast with Bellomo et al. who found no association between mean protein provision and 90-day mortality in a large cohort ($n = 1457$) of CRRT-receiving ICU patients. However, protein provision in their study population was very low (mean value of 0.5 g/kg/day with only 10% of patients receiving >1.0 g/kg/day) and these results were not adjusted for relative energy provision and sepsis [11]. However, as protein provision up to 2.5 g/kg/day is recommended in CRRT-receiving patients, protein provision of 1.2 g/kg/day in the current study is also still below the recommended amount [23]. Doig et al. performed a randomized controlled trial in ICU patients with both normal kidney function, kidney dysfunction and/or risk of progression of acute kidney injury (AKI). For the total group, no effect on 90-day mortality was observed when administering intravenous (IV) AAs upto 2.0 g/kg/day (actual protein provision 1.7 g/kg/day) during ICU admission [24]. However, in a post hoc analysis of this study (including still 85% of the original study population for both arms), they showed that 90-day mortality was substantially lower in patients receiving early AA infusions when baseline kidney function was normal [25]. Therefore, early high protein provision appears to lower mortality in ICU patients, with a modulating role for kidney function. It is quite interesting to note that in the excluded patient group, including baseline kidney dysfunction and/or risk of progression of AKI, the mortality in the AA infusion group was double the reference group. In other words, the effect was in fact reversed, explaining the absence of the intravenous AA infusion effect in the total study group. Zhu et al. [25] explains the effect by providing a sufficient dose of the branched-chain AA leucine, isoleucine, and valine and their stimulation of mitochondrial biogenesis by activating the mTOR pathway [26, 27]. Mitochondrial biogenesis refers to the adaptive process of growth and replication undertaken by mitochondria in response to an increased need for adenosine triphosphate production during metabolic stress. The AA infusion was commenced on the first or second day of ICU stay, which shows that early stimulation of mitochondrial biogenesis through the mTOR pathway is a plausible mechanism of action. In the current study we have less information on kidney dysfunction other than the need for CRRT. However, we now confirm that in these patients, with both pre-existing and newly onset kidney dysfunction, the higher level of protein provision was also inversely associated with mortality. For an unknown cause, the baseline existance of kidney dysfunction prohibits this positive effect. Patients were included in the CRRT-receiving group when treated with CRRT for at least 24 h in the first 4 days of ICU stay, but still generated a positive outcome. Admittedly, in the sensitivity analysis including only patients receiving more than 50% of their estimated energy requirement, significance of the association between early high protein and mortality was lost. Partly the power of the analysis declines for statistical assertions, however other currently unknown factors may come into play.

Here we confirm earlier observations of a significant association between protein intake and lower mortality in non-septic patients [4, 28]. We also confirm our earlier observation that there is no association between early protein intake and mortality in septic patients at the higher recommended level of ≥1.2 g/kg/day [4]. De Koning et al. showed higher 6-month mortality in septic patients receiving ≥1.2 g/kg/day compared to 0.8–1.2 g/kg/day protein at day 4 to 7 [28]. Even so, Elke et al. showed that higher protein intake, but below recommended level of 1.2 g/kg/day, was associated with lower mortality in a large cohort of septic patients

[29]. Animal studies have shown that sepsis is associated with an inhibition of the kinase B and complex 1 mTOR pathway, which are responsible for both preventing muscle breakdown and promoting protein synthesis [30, 31]. A possible explanation therefore would be that the biological system cannot handle this level of AA supply. It is not necessarily causing a detrimental effect, however there appears to be no anabolic stimulus. At the same time, autophagy might be compromised in septic patients to larger extend than in other patient groups, tipping the balance of positive effects to absent effect of early high protein feeding.

Our study has several strengths. To the best of our knowledge, this is the first study describing the beneficial effect of early high protein provision in CRRT-receiving patients. A fairly large sample size was studied, which increases reliability of the results. Furthermore, energy derived from propofol and glucose infusions were taken into account. In the Cox regression analysis we adjusted for severity of illness, BMI and age as well as for energy overfeeding, a known inhibitor of the effect [4, 22]. Results for the total group, non-septic patients and septic patients remained robust when performing sensitivity analysis in patients receiving energy >50%, which indicates that the results are robust at higher intakes and are not explained by lower intake and higher mortality due to more severe illness [32–34]. The retrospective design and single center nature of this study are a limitation. Data on sepsis on admission were missing in a large number of patients, limiting the sample size of analyzed subgroups and thereby generalizability. Especially the use of an equation for energy expenditure instead of indirect calorimetry measurements limits the reliability of the energy requirement adjustments since it is known that equations have limited accuracy.

In conclusion, early (day 4) high protein provision is associated with lower hospital and ICU mortality in ICU patients, including CRRT-receiving patients. For septic patients, we confirm that this association is not observed. Early high protein provision therefore appears to be beneficial for survival of ICU patients. Nonetheless, randomized controlled trials should be conducted, focusing on patient subgroups like CRRT-receiving patients and septic patients since these groups are expected to have deviating protein requirements. These studies will improve guidelines by leading to personalized protein recommendations in ICU patients.

REFERENCES

1. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310:1591–600.
2. Weijs PJM, Looijaard WGPM, Dekker IM, Stapel SN, Girbes AR, Oudemans-van Straaten HM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. Crit Care. 2014;18:R12.
3. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013;17:R206.
4. Weijs PJM, Looijaard WGPM, Beishuizen A, Girbes ARJ, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care. 2014;18:701.
5. Allingstrup MJ, Esmailzadeh N, Knudsen AW, Espersen K, Jensen TH, et al. Provision of protein and energy in relation to measured requirements in intensive care patients. Clin Nutr. 2012;31:462–8.
6. Bendavid I, Zusman O, Kagan I, Theilla M, Cohen J, Singer P. Early administration of protein in critically ill patients: a retrospective cohort study. Nutrients. 2019;11:106.
7. Koekkoek WAC, van Setten CH, Olthof LE, Kars JCN, van Zanten ARH. Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: the PROTINVENT retrospective study. Clin Nutr. 2019;38:883–90.
8. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38:48–79.
9. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. J Parenter Enter Nutr. 2016;40:159–211.
10. Honore P, Honoré PM, De Waele E, Jacobs R, Mattens S, Rose T, et al. Nutritional and Metabolic Alterations during Continuous Renal Replacement Therapy. Blood Purif. 2013;35:279–84.
11. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lee J, et al. Daily protein intake and patient outcomes in severe acute kidney injury: findings of the randomized evaluation of normal versus augmented level of replacement therapy (RENAL) trial. Blood Purif. 2014;37:325–34.
12. Scheinkestel CD, Kar L, Marshall K, Bailey M, Davies A, Nyulasi I, et al. Prospective randomized trial to assess caloric and protein needs of critically Ill, anuric, ventilated patients requiring continuous renal replacement therapy. Nutrition. 2003;19:909–16.
13. Gunst J. Recovery from critical illness-induced organ failure: the role of autophagy. Crit Care. 2017;21:209.
14. Feng Y, Liu B, Zheng X, Chen L, Chen W, Fang Z. The protective role of autophagy in sepsis. Microb Pathogenesis. 2019;131:106–11.
15. de Koning M-SLY, Koekkoek WAC, Kars JCN, van Zanten ARH. Association of PROtein and CAloric Intake and Clinical Outcomes in Adult SEPTic and Non-Septic ICU Patients on Prolonged Mechanical Ventilation: The PROCASEPT Retrospective Study. J Parenter Enter Nutr. 2019;44:434–43.
16. Thoral PJ, Peppink JM, Driessen RH, Sijbrands EJG, Kompanje EJO, Kaplan L, et al. on behalf of the Amsterdam University Medical Centers Database (AmsterdamUMCdb) Collaborators and the SCCM/ESICM Joint Data Science Task Force (2021). Sharing ICU Patient Data Responsibly Under the Society of Critical Care Medicine/European Society of Intensive Care Medicine Joint Data Science Collaboration: The Amsterdam University Medical Centers Database (AmsterdamUMCdb) Example. Crit Care Med 2021;49:e563–77. https://doi.org/10.1097/CCM.0000000000004916.
17. Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. Am J Clin Nutr. 1984;40:168–82.
18. Weijs PJM, Stapel SN, de Groot SDW, Driessen RH, de Jong E, Girbes ARJ, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically Ill patients. J Parenter Enter Nutr. 2012;36:60–8.
19. Singer P, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med. 2011;37:601–9.
20. Abd El Sabour Faramawy M, Abd Allah A, El Batrawy S, Amer H. Impact of high fat low carbohydrate enteral feeding on weaning from mechanical ventilation. Egypt J Chest Dis Tuberculosis. 2014;63:931–8.
21. El Koofy NM, Rady HI, Abdallah SM, Bazaraa HM, Rabie WA, El-Ayadi AA. The effect of high fat dietary modification and nutritional status on the outcome of critically ill ventilated children: single-center study. Korean J Pediatr. 2019;62:344–52.
22. Looijaard WG, Dekker IM, Beishuizen A, Girbes AR, Oudemans-van Straaten HM, Weijs PJ. Early high protein intake and mortality in critically ill ICU patients with low skeletal muscle area and-density. Clin Nutr. 2019;39:2192–201.
23. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically Ill patient. J Parenter Enter Nutr. 2009;33:277–316.
24. Doig GS, Simpson F, Bellomo R, Heighes PT, Sweetman EA, Chesher D, et al. Intravenous amino acid therapy for kidney function in critically ill patients: a randomized controlled trial. Intensive Care Med. 2015;41:1197–208.
25. Zhu R, Allingstrup MJ, Perner A, Doig GS, for the Nephro-Protective Trial Investigators G. The effect of IV amino acid supplementation on mortality in ICU patients may be dependent on kidney function: post hoc subgroup analyses of a multicenter randomized trial. Crit Care Med. 2018;46:1293–301.
26. Zhang L, Han J. Branched-chain amino acid transaminase 1 (BCAT1) promotes the growth of breast cancer cells through improving mTOR-mediated mitochondrial biogenesis and function. Biochem Biophys Res Commun. 2017;486:224–31.
27. Weichhart T. Mammalian target of rapamycin: a signaling kinase for every aspect of cellular life. Methods Mol Biol. 2012;821:1–14.
28. de Koning M-SLY, Koekkoek WAC, Kars JCN, van Zanten ARH. Association of PROtein and CAloric intake and clinical outcomes in adult SEPTic and non-septic ICU patients on prolonged mechanical ventilation: the PROCASEPT retrospective study. J Parenter Enter Nutr. 2020;44:434–43.
29. Elke G, Wang M, Weiler N, Day AG, Heyland DK. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. Crit Care. 2014;18:R29.
30. Stana F, Vujovic M, Mayaki D, Leduc-Gaudet J-P, Leblanc P, Huck L, et al. Differential regulation of the autophagy and proteasome pathways in skeletal muscles in sepsis. Crit Care Med. 2017;45:e971–9.
31. Sandri M. Autophagy in skeletal muscle. FEBS Lett. 2010;584:1411–6.
32. Preiser J-C, van Zanten ARH, Berger MM, Biolo G, Casaer MP, Doig GS, et al. Metabolic and nutritional support of critically ill patients: consensus and controversies. Crit Care . 2015;19:35.

33. Heyland DK, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake!*. Crit Care Med. 2011;39:2619–26.
34. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009;35:1728–37.

ACKNOWLEDGEMENTS

We thank Ronald Driessen, Department of Adult Intensive Care Medicine, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, the Netherlands, for his contribution.

AUTHOR CONTRIBUTIONS

IR, SS, and PW designed the study. IR obtained the data, performed statistical analysis, and drafted the paper. SS and PW coordinated the study. SS, PW, and AG helped to draft the paper. All authors read and approved the final paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41430-022-01103-8.

Correspondence and requests for materials should be addressed to Peter J. M. Weijs.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.