



Original article

Prospective observational cohort study of reached protein and energy targets in general wards during the post-intensive care period: The PROSPECT-I study



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SUMMARY

Introduction: Nutrition plays an essential role in the recovery of critical illness. In the post-Intensive Care Unit (ICU) period, patients typically return to oral nutrition gradually. However, studies quantifying nutritional intake in the post-ICU hospitalization period are scarce and formal guidelines are lacking. This study aims to describe energy and protein intake in detail over the entire post-ICU hospitalization period and explore associations between protein intake and clinical outcomes.

Methods: A prospective observational single-center cohort study was conducted amongst post-ICU patients in general wards after a minimum ICU-stay of 72 h and who received (par)enteral feeding for ≥ 24 h in the ICU. Oral intake was assessed daily using food order lines and digital photography of meal leftovers. Other data, including amounts of (par)enteral nutrition, were collected from electronic medical records. The primary outcome was to identify energy and protein intake, and reached targets, in the post-ICU period. In addition, length of hospital stay after ICU discharge, readmission and mortality rates were compared between patients meeting protein targets or not.

Results: In total, 48 patients were included. Complete nutritional data of 34 patients were analyzed in the current study, adding up to a total number of 484 observational days, 1681 photos and 6634 food order lines. Inter-rater agreement was excellent (ICC 0.878). Overall mean energy and protein adequacy for all nutritional groups was 82.3% (SD 18.3) and 83.1% (SD 19.8). Only 51.2% of the study participants ($n = 21$) reached overall $>90\%$ of prescribed protein targets during their entire post-ICU ward stay. The lowest intake was seen in the patient group with exclusively oral intake (median protein adequacy 75.5%), whereas patients with (supplemental) enteral nutrition (EN) all met $>90\%$ of their protein targets. Prescribed targets were below recommendations, and prescribed calories and proteins were neither ordered nor consumed. Discontinuation of EN resulted in immediate marked drops in energy (44.1%) and protein intake (50.7%). Subsequently, patients needed up to six days to reach protein targets again. No differences in clinical outcomes were observed.

Conclusion: Most patients did not meet energy and protein targets in the post-ICU hospitalization period. Nutrition performance was highly dependent on the route of nutrition and was lowest among patients with oral intake only (despite of food fortification strategies and/or oral nutritional supplements). The best intake was observed in patients receiving (supplemental) EN. However, cessation of EN posed an immediate nutritional risk. No differences in clinical outcomes were found in this study. Our findings stress the need for follow-up studies to close the gap with individualized nutritional support in the post-ICU period to reach protein and energy targets.

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List of abbreviations

APACHE II	Acute Physiology And Chronic Health Evaluation II
AYR	At Your Request®
BMI	Body Mass Index
CPAX	Chelsea Critical Care Physical Assessment tool
EN	Enteral Nutrition
FAO/WHO/UNU	Food and Agricultural Organization and World Health Organization
IBW	Ideal Body Weight
ICU	Intensive Care Unit
IQR	Interquartile Range
LOS	Length Of Stay
MRC	Medical Research Council
NUTRIC	Nutrition Risk In Critically ill
ONS	Oral Nutrition Supplements
PDMS	Patient Data Management System
PN	Parenteral Nutrition
RCT	Randomized Controlled Trial
SAPS II	Simplified Acute Physiology Score
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
ZGV	Gelderse Vallei Hospital

1. Introduction

Nutrition plays a crucial role in the recovery of critical illness. Appropriate nutritional intake, in particular protein (≥ 1.3 g/kg*day [1]), in critically ill patients in the Intensive Care Unit (ICU) is associated with a decreased hospital length of stay (LOS), morbidity and mortality [2–6]. However, critically ill patients are often unable to feed themselves. Therefore, enteral nutrition (EN) and/or parenteral nutrition (PN) are regularly administered in the ICU [1]. In the (post-ICU) recovery period from critical illness, it is expected that patients return to oral nutrition gradually. This transition is often combined with supplemental EN or PN. Furthermore, food fortification strategies, such as energy- and protein-enriched foods or oral nutrition supplements (ONS), are frequently used. Nevertheless, formal guidelines for the dynamic nutritional targets of post-ICU patients are lacking. Guidelines that may be suitable for these patients recommend a caloric intake of 25–30 kcal/kg*day and a protein intake of about 1.5 g/kg*day [7,8]. However, during the recovery phase of critical illness, patients' metabolic targets and physical mobility increase significantly [9–12]. Thus, it may be suggested that their energy expenditure will exceed the recommended energy and protein intake. Inadequate nutrition in this phase will lead to poor recovery [13]. Therefore, optimizing protein and energy intake is essential to attenuate further loss of lean body mass and promote recovery of physical functioning and quality of life [10–12].

Current literature assessing nutritional performance in the post-ICU period in general wards is scarce [14]. Ridley et al. demonstrated that energy and protein intake remained below predicted targets [15]. The lowest intake was observed in the patients with exclusively oral intake, while patients with total EN did not demonstrate a deficit in energy and protein intake. This observation is in line with Moisey et al., who examined the nutritional intake of 19 critically ill patients in the first week after extubation [16]. A study conducted among 37 patients with moderate traumatic brain injury by Chapple et al. showed similar results, although energy and protein deficits in patients on solely EN were also demonstrated [17]. Collectively, these studies

suggest that nutritional follow-up and strategies to enhance intake during the phase after critical illness are necessary, although the evidence is limited [14,18,27]. Sample sizes were small, nutritional intake was not assessed daily, and PN was not considered [15,17]. Furthermore, it is unknown whether nutritional intake in the post-ICU hospitalization period is associated with clinical outcomes, such as length of hospital stay, morbidity and mortality. In a multicenter trial outside critical care, it has been demonstrated that individualized nutritional support results in enhanced energy and protein intake and lowers the risk of 30-day adverse outcomes and mortality [14,19].

This present study describes a complete representation of the energy and protein intake over the entire post-ICU hospitalization period, with a specific interest in energy and protein intake and reached targets between patients with different nutritional routes (oral, EN and/or PN). Secondary study endpoints included length of hospital stay after ICU discharge, discharge destinations, readmission, and mortality rates. We hypothesize that adequate nutrition in the post-ICU period may positively impact clinical outcomes. The findings from the proposed work will yield new insight into nutritional intake during the post ICU-period.

2. Materials and methods

2.1. Study design

A prospective observational single-center cohort study was conducted from 6 May 2019 to 16 March 2020 in patients who were discharged from a mixed medical-surgical ICU to a general ward of Gelderse Vallei hospital (ZGV, Ede, The Netherlands). Study inclusions were ended unexpectedly early due to the outbreak of the COVID-19 pandemic.

2.2. Study participants

Critically ill adult patients (aged ≥ 18 years) who were ready for ICU discharge after an ICU-stay of ≥ 72 h and who received (par) enteral feeding for ≥ 24 h during ICU stay were eligible for inclusion. Any patient who received exclusively oral nutrition during ICU stay was excluded, since we were interested in patients who underwent a transition in nutritional mode. Moreover, patients on exclusive oral nutrition were thought to have lower disease acuity, and it is likely that these patients can ramp-up oral feeding more rapid after ICU discharge than patients on (prolonged) medical nutrition.

Additionally, anyone who was not discharged to a general ward in our hospital was excluded, as were patients who had a life-expectancy of < 48 h. Until August 2019, patients who were discharged to a non-surgical ward were excluded as well, as there was no permission for study assessments in these wards at the start of the study (hereafter indicated with “non-PROSPECT ward”). After obtaining informed consent from the patient or legal representative, eligible patients were enrolled in consecutive order.

2.3. Clinical data collection

Data collection from the electronic Patient Data Management System (PDMS) included patient characteristics (age, gender, anthropometry, comorbidities), admission type, several scores (Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS II), Nutrition Risk In Critically ill (NUTRIC)), and outcome parameters, such as length of ICU and hospital stay (LOS), 3-, 6- and 12-month readmission and mortality rates. On the day of ICU and hospital discharge, start and end of study

assessments were performed, including assessment of swallowing function and physical performance (using the Medical Research Council (MRC) scale for global muscle strength evaluation and Chelsea Critical Care Physical Assessment tool (CPAx)).

Data extraction was performed using queries searching the ICU PDMS (MetaVision; iMDsoft, Tel Aviv, Israel) and electronic patient record system (NeoZis; MI Consultancy, Katwijk, The Netherlands). The National Population Register was consulted for death records. Data verification was conducted manually. All parameters of interest, except for assessment of physical performance, had been routinely collected during standard clinical care, and therefore imposed no burden or risk to patients.

2.4. Nutritional assessment

The study started on the day of ICU discharge (day 0). Days were defined as calendar days.

From the first study day onwards until hospital discharge, type of nutrition (oral, EN, PN, or a combination thereof) as well as total energy (in kcal/day) and protein (in g/day) intake were recorded daily (see Supplement 1). Small amounts of food or sips of water to assess swallowing function were not considered oral intake. Quantifications of nutrition were used to calculate the percentage of reached energy and protein targets (hereafter indicated with “adequacy”), as set by the dietitians. Timing and reason of discontinuation or start of (par)enteral nutrition was recorded, as well as removal of a feeding tube or central venous catheter. Study assessments and data collection were stopped when death was imminent. The intake on (ICU and hospital) discharge days were excluded from final nutritional analyses.

In case of readmission to the ICU, only the nutritional data after ICU readmission were analyzed.

2.5. Assessment of oral intake

To quantify oral nutrition, pictures of meal leftovers were assessed. All study participants were discharged from the ICU with a digital camera attached to their beds and study placemats on their meal trays. Post-meal photos were taken by general ward nurses and food service assistants. Two researchers (RSB and LD/SM) analyzed these pictures independently after the patient finished study participation. These pictures were compared to pre-meal images of serving portions, which were made by one researcher (NS) under precisely similar conditions before the start of the study [20]. The amount of food consumed was graded with 0 (indicating nothing consumed) - 0.25–0.375 - 0.5–0.625 - 0.875 - or 1 (indicating entire meal consumed). Discrepancies in the assessment were resolved by discussion. In case of missing products in the pictures, missing data were extrapolated using intake data of that specific meal or day. If this was not possible due to too many missings, data were imputed using nursing report sheets and digital food record charts. If this could not be obtained, missing meal data were excluded from nutritional analyses.

Oral intake assessments were compared to the database with food order lines from At Your Request® (AYR). AYR is a hospital meal service offering patients the possibility to order from a menu card throughout the day between 7 a.m. and 7 p.m. by placing a telephone call [21]. The operators from the call center are aware of the patients’ diets and might help them choose from the menu. Kitchen staff prepare and serve the ordered food in standardized serving sizes, which are delivered within 45 min to the patients. All food orders (per patient per day) are automatically stored in the Menu Management System, including information about macronutrients (calories and proteins).

Patients, hospital staff, family and visitors were kindly asked to list all additional nutrition not ordered from AYR on a food intake chart.

2.6. Assessment of (par)enteral nutrition

Data regarding calories and proteins from administered (par) enteral nutrition were collected manually from the PDMS.

2.7. Calculation of targets

Energy and protein targets were calculated by the dietitians using the Food and Agricultural Organization and World Health Organization [22] formulas, adapted for specific patient groups (such as chronic kidney disease or dialysis) according to the local hospital protocol for nutritional support (see Supplement 2) (FAO/WHO/UNU). Patient’s weight on ICU admission was used for these calculations, as measured using bedscales. Weight of patients with a Body Mass Index (BMI) of <18.5 or >27 kg/m² was adjusted to ideal body weight (IBW) at a BMI of 18.5 or 27 kg/m². Energy and protein targets on the day of ICU and hospital discharge were adjusted for the actual time spent in the ICU and ward these days, respectively.

The role of the dietitians in this study was not different from general practice in our hospital. Nutritional prescriptions of post-ICU patients are reviewed two times per week by dietitians. In case of insufficient oral intake, patients were provided with dietitian advice to match preferences and needs, and/or prescribed food fortification strategies, ONS or tube feeding.

2.8. Study outcomes

The primary objective of this study was to assess energy and protein intake expressed as a percentage of calculated targets (adequacy) between patients with oral, enteral, parenteral, or combined nutrition in general wards during the post-ICU hospitalization period.

The secondary objective was to explore differences in outcomes such as length of hospital stay after ICU discharge, discharge destinations, readmission, and mortality rates between protein intake groups. Protein intake groups were based on achieving less or more than 90% of the protein targets during ward stay. Clinical outcomes of the low (<90% of targets) versus the high (>90%) intake groups were compared. A composite endpoint of unfavourable outcome was composed of hospital readmission within six months or 6-month mortality.

2.9. Statistical analysis

Discrete variables were reported as proportions. Continuous data were expressed in means including standard deviations (SD) or, in the case of non-parametric data, as medians with interquartile ranges (IQR). P-values for continuous outcome variables were calculated using paired t-tests, two-sample t-tests or one-way ANOVA, or in case of non-normal distribution, Wilcoxon signed-rank, Mann–Whitney U or Kruskal Wallis tests where appropriate. Crosstabs were assessed using the Chi–Square test; the Fisher Exact test was used when cell counts were lower than 5. P-values below 0.05 were considered statistically significant. P-values <0.10 were considered trends. An intraclass correlation coefficient (ICC) was computed to evaluate agreement between two researchers in the assessment of digital pictures to quantify oral intake (two-way random effects model). Inter-rater agreement was considered poor with an ICC <0.4, fair when 0.4 ≤ ICC <0.6, good when 0.6 ≤ ICC <0.8 and excellent when ICC was ≥0.8.

The composite endpoint (6-month hospital readmission or mortality) was assessed by Kaplan Meier curves and Cox Proportional Hazards Regression Analysis. All relevant variables based on current literature were included in the univariable Cox regression analysis. Furthermore, variables with a p-value <0.10 and which were deemed clinically relevant were included in multivariable Cox regression analyses.

All statistical analyses were conducted using IBM SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA; 2016). Normality was assessed numerically and graphically (visual inspection of histograms and Q–Q plots).

2.10. Ethical approval

The ethical approval committee approved the study of ZGV (study protocol number 1810-181).

3. Results

A total of 626 patients were discharged from our ICU during the study period, of whom 121 were eligible for inclusion (see Fig. 1). Of these, 48 patients were enrolled in the study.

The baseline characteristics of the included and analyzed patients are summarized in Table 1. The patient group who received (supplemental) PN (n = 3) at ICU discharge consisted of surgical patients only (p = 0.06). A trend toward lower APACHE II, SOFA, SAPS II and NUTRIC scores (p < 0.01) was seen in this patient group.

3.1. Nutritional assessment

Due to technical problems with photo cameras, the nutritional data of five patients could not be analyzed, and two patients were

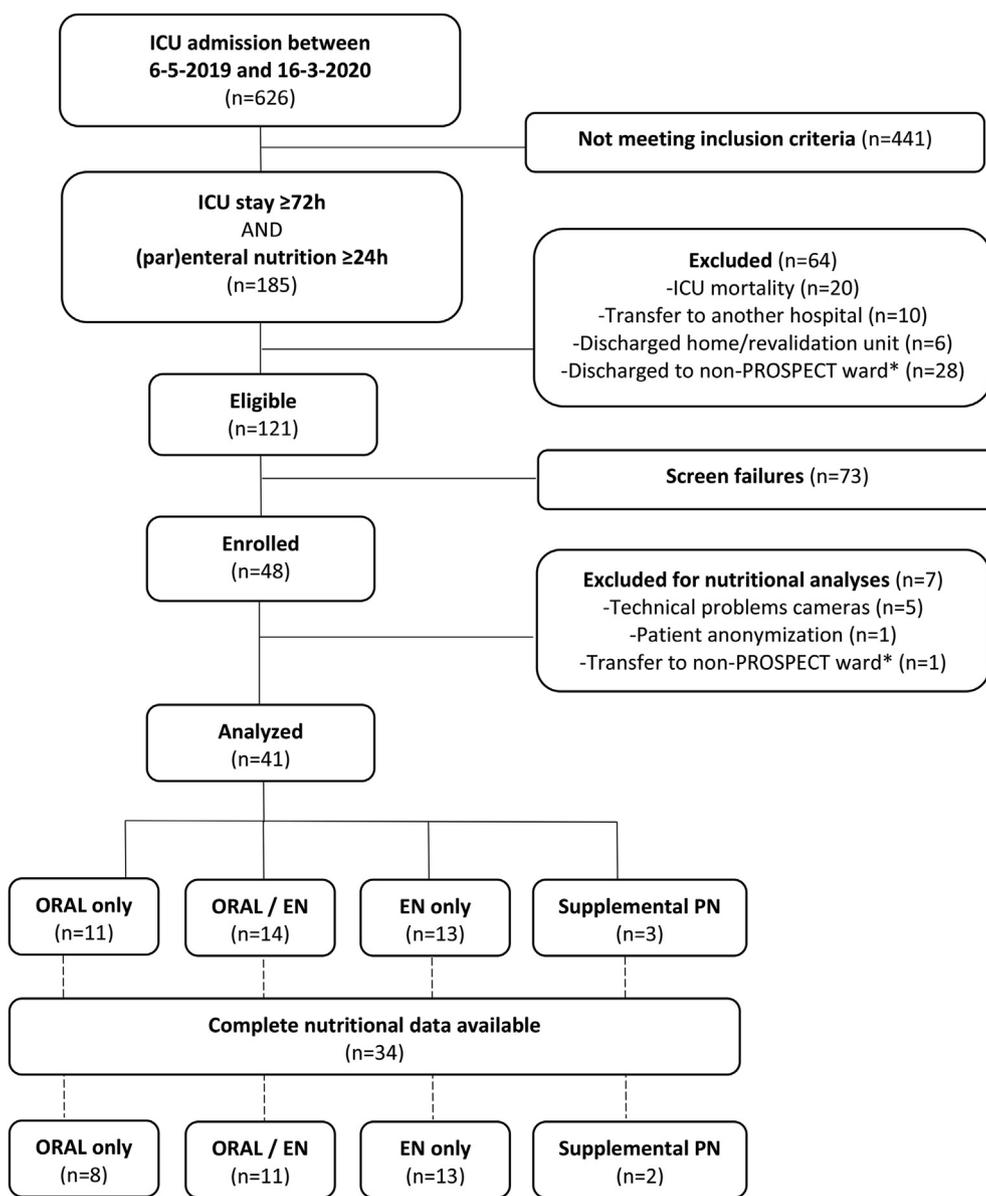


Fig. 1. Study flowchart. Legend: ICU = Intensive Care Unit; ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition; *non-PROSPECT ward: patients who were discharged to a medical ward could only be included from August 2019 onwards, as there was no permission for study assessments in these wards at the start of the study.

Table 1
Baseline characteristics.

		All patients (n = 41)	ORAL only ^a (n = 11)	ORAL/EN ^a (n = 14)	EN only ^a (n = 13)	PN ± EN ± ORAL ^a (n = 3)	p-value ^b
Gender (male)	N (%)	19 (46.3)	5 (45.5)	6 (42.9)	6 (46.2)	2 (66.7)	0.517
Age (years)	mean (SD)	70.8 (11.4)	70.0 (10.9)	71.3 (10.9)	70.9 (13.9)	70.7 (9.5)	0.908
BMI on ICU admission (kg/m ²)	mean (SD)	26.7 (6.0)	27.8 (7.3)	24.6 (6.0)	27.3 (4.4)	29.2 (7.0)	0.241
APACHE II score on ICU admission	mean (SD)	20.4 (6.7)	23.2 (6.7)	20.4 (7.6)	19.2 (5.4)	15.3 (4.7)	0.348
SOFA score on ICU admission	mean (SD)	6.6 (2.8)	7.4 (3.8)	6.6 (2.5)	6.3 (2.3)	5.0 (2.0)	0.770
SAPS II score	mean (SD)	43.2 (13.4)	46.3 (17.5)	43.9 (11.9)	43.7 (9.8)	27 (10)	0.210
NUTRIC score	mean (SD)	5.0 (1.4)	5.4 (1.9)	4.7 (1.1)	5.2 (1.4)	4.0 (1.0)	0.486
Admission type (non-surgical)	N (%)	23 (56.1)	9 (81.8)	9 (64.3)	5 (38.5)	0 (0)	0.066

Legend. BMI = Body Mass Index; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; SAPS II = Simplified Acute Physiology Score; NUTRIC = Nutrition Risk in Critically ill; N = number; IQR = InterQuartile Range; SD = Standard Deviation.

^a Nutritional route at ICU discharge: ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition.

^b p-values were calculated using the Fisher Exact test or one-way ANOVA where appropriate.

Table 2
Nutritional data - overview.

		All patients (n = 41)	ORAL only ^a (n = 11)	ORAL/EN ^a (n = 14)	EN only ^a (n = 13)	PN ± EN ± ORAL ^a (n = 3)	p-value ^c
Nutritional route at hospital discharge	N (%)						<0.001**
ORAL only		28 (68.3)	11 (100)	10 (71.4)	6 (46.2)	1 (33.3)	
ORAL + EN		7 (17.1)	0 (0)	4 (28.6)	3 (23.1)	0 (0)	
EN		3 (7.3)	0 (0)	0 (0)	3 (23.1)	0 (0)	
PN + ORAL		1 (2.4)	0 (0)	0 (0)	0 (0)	1 (3.3)	
Not appropriate (in-hospital death)		2 (4.9)	0 (0)	0 (0)	1 (7.7)	1 (3.3)	
Swallowing function at ICU discharge	N (%)						0.012**
Good		28 (68.3)	11 (100)	11 (78.6)	3 (23.1)	3 (100)	
Moderate		10 (24.4)	0 (0)	2 (14.3)	8 (61.5)	0 (0)	
Bad		3 (7.3)	0 (0)	1 (7.1)	2 (15.4)	0 (0)	
Jejunal feeding tube at ICU discharge (yes)	N (%)	4 (9.8)	0 (0)	1 (7.1)	2 (15.4)	1 (33.3)	0.024**
Energy target in ward (kcal/kg IBW ^a day)	median [IQR]	27.8 [26.3–29.3]	28.2 [26.8–30.6]	27.9 [26.4–30.4]	26.9 [25.9–28.3]	31 [28–42]	0.163
Energy intake (kcal/kg IBW ^a day ^b)	mean (SD)	24.7 (7.5)	24.2 (6.2)	25.9 (9.8)	24.1 (6.4)	23.7 (7.1)	0.963
Adequacy to target (%)		82.3 (18.3)	81.7 (15.9)	82.5 (19.5)	85.9 (19.8)	69.9 (14.3)	0.604
Protein target in ward (g/kg ^a day)	N (%)						0.078
1.2 g/kg ^a day		5 (12.2)	3 (27.3)	0 (0)	1 (7.7)	1 (33.3)	
1.2–1.5 g/kg ^a day		12 (29.3)	4 (36.4)	4 (28.6)	4 (30.8)	0 (0)	
1.5 g/kg ^a day		24 (58.5)	4 (36.4)	10 (71.4)	8 (61.5)	2 (66.7)	
Protein intake (g/kg IBW ^a day ^b)	mean (SD)	1.25 (0.38)	1.15 (0.35)	1.31 (0.45)	1.27 (0.33)	1.22 (0.47)	0.864
Adequacy to target (%)		83.1 (19.8)	79.1 (14.5)	82.8 (21.9)	85.6 (20.8)	80.9 (30.1)	0.752
Overall averaged energy adequacy >90%	N (%)	20 (48.8)	4 (36.4)	8 (57.1)	8 (61.5)	0 (0)	0.311
Overall averaged energy adequacy >100%	N (%)	11 (26.8)	3 (27.3)	5 (35.7)	3 (23.1)	0 (0)	0.778
Overall averaged protein adequacy >90%	N (%)	21 (51.2)	3 (27.3)	8 (57.1)	8 (61.5)	2 (66.7)	0.376
Overall averaged protein adequacy >100%	N (%)	14 (34.1)	2 (18.2)	6 (42.9)	5 (38.5)	1 (33.3)	0.358

Legend. ICU = Intensive Care Unit; IBW = ideal bodyweight; N = number; IQR = InterQuartile Range; SD = Standard Deviation; NA = not appropriate.

** p-value <0.05.

^a Nutritional route at ICU discharge: ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition.

^b Average during hospital stay after ICU discharge; all nutritional routes (oral, EN, PN, or mixed).

^c p-values were calculated using Fisher Exact test, Kruskal Wallis test or one-way ANOVA where appropriate.

excluded from further analyses due to patient anonymization and transferal to a non-PROSPECT ward. An overview of nutritional parameters of the 41 evaluable patients is depicted in Table 2. From 34 patients (82.9%), nutritional intake during the entire study participation could be analyzed. From seven patients (17.0%) incomplete data was available (median 4 [IQR 2–9] days); only twenty-eight out of 60 days could be analyzed due to missing data. The number of observational days after ICU discharge (and thus length of ward stay) was median 12 [IQR 8–15] days. No food record charts that reported food not registered by AYR, such as food brought in by family members, were retrieved. A total number of 484 study days were analyzed, including 1681 post-meal photos and 6634 order lines from AYR. There was excellent agreement between the two researchers in the assessment of pictures to quantify oral intake (ICC 0.878). Mean difference was 0.7 kilocalories and 0.02 g of protein per product ordered.

Nutritional routes at ICU discharge varied between oral intake only (n = 11 (26.8%); 123 study days), EN only (n = 13 (31.7%); 177 days), combined oral/EN (n = 14 (34.1%); 152 days) or supplemental PN (n = 3 (7.3%); 32 days). At hospital discharge, most patients had exclusively oral intake (n = 28; 68.3%). Ten patients (24.4%) were discharged with (supplemental) EN, and one patient (2.4%) with supplemental PN.

Dietician energy targets for the PN group were, on average, higher than the other nutritional groups, although not statistically significant (p = 0.071), mainly due to a single patient whose target was set at 3300 kcal/day (42 kcal/kg IBW*day) to compensate for intestinal losses. Most patients were prescribed a protein target of 1.5 g/kg*day (n = 24; 58.5%). Mean energy and protein intake averaged over all study days for all nutritional groups was 24.7 (standard deviation (SD) 7.5) kcal/kg IBW*day and 1.25 (SD 0.38) g/kg IBW*day respectively, corresponding to 82.3% (SD 18.3) and

83.1% (SD 19.8) of reached targets, respectively. Twenty-one patients (51.2%) had overall protein adequacy above 90% during their ward stay after ICU discharge. Of note, all patients (100%) with oral nutrition, received food fortification and/or ONS.

3.2. Oral nutrition only

The patients with oral nutrition only at ICU discharge ($n = 11$) had a median overall energy intake during ward stay of 22.3 [IQR 18.8–29.3] kcal/kg IBW*day, corresponding to median adequacies of 82.2% [IQR 66.4–100] ($p = 0.037$) (Table 3A, Supplement 4B). Four patients (36.4%) had an average overall energy adequacy above 90%. Of note, in patients not reaching energy targets (adequacy <90%; intake median 19.7 [IQR 17.9–22.1] kcal/kg IBW*day), the amount of energy ordered was significantly below target prescriptions (median 25.4 [IQR 23.8–26.2] versus 28.1 [26.3–29.4] kcal/kg IBW*day; $p = 0.018$) (Table 3B).

The median protein intake was 1.07 [IQR 0.90–1.35] g/kg IBW*day. This corresponded to median adequacies of 75.5% [IQR 69.1–94.7]. Three (27.3%) patients had an overall average adequacy of >90% regarding protein intake. Also, in patients not reaching protein prescriptions (adequacy <90%; intake median 0.92 [IQR 0.84–1.13] g/kg IBW*day), the amount of protein ordered was statistically significant less than prescribed (median 1.17 [IQR 1.15–1.27] versus 1.33 [1.23–1.50] g/kg IBW*day; $p = 0.018$).

Details of nutritional intake in patients with adequacies below 100% are shown in Supplement 3.

3.3. Transition from (supplemental) EN to oral nutrition only

During ward stay, 16 patients (53.3%) went through a transition from (supplemental) EN to exclusively oral nutrition. These patients received median 3 [IQR 1–5] days of (supplemental) EN before discontinuation. Reasons to stop EN included (supposed) sufficient oral intake ($n = 13$), inadvertent removal of feeding tube ($n = 2$), or patient refusal ($n = 1$). Median overall averaged energy and protein adequacy before the stop of EN was 97.3% [IQR 77.3–119.8] and 91.5% [78.0–142.4], respectively. The performance dropped to an overall average adequacy of median 76.0% [IQR 63.0–88.9] and 75.4% [55.2–101.7] after the discontinuation of EN support. A statistically significant increase in energy and proteins ordered was seen after discontinuation of enteral feeding ($p = 0.008$), although this was not enough to reach prescribed targets (median adequacy to energy and protein target: 81.8% and 90.4%, respectively).

The largest drop in intake was seen at day 1 after discontinuation of EN (median energy intake 17.4 [IQR 15.9–31.0] kcal/kg IBW*day (adequacy 65.0% [50.3–102.0]); median protein intake 0.97 [0.80–1.52] g/kg IBW*day (adequacy 60.6% [53.6–104.3])) (Fig. 2). After this, an increase in energy intake was seen until day 6 to median 22.3 [16.5–28.4] kcal/kg IBW*day (adequacy median

75.2% [IQR 57.0–112.2]) and protein intake to 1.36 [0.66–1.64] g/kg IBW*day (adequacy median 103.2% [44.1–118.6]). A second drop of energy and protein intake was seen at day 7 in the patients who were not discharged from the hospital yet, as shown in Table 4, although not statistically significant ($p = 0.068$ and 0.144, respectively).

Separate analyses were performed for patients with <100% protein adequacy both before and after discontinuation of EN; these results are shown in Supplement 6.

The patient group who discontinued EN because of (supposed) sufficient intake ($n = 13$) had overall median energy and protein adequacies of 99.8% [IQR 66.4–133.5] and 95.4% [78.8–155.7] before discontinuation, although five of them (38.5%) had an overall median protein adequacy <90% (Supplement 6).

After discontinuation, the median average overall energy and protein adequacies until hospital discharge were 77.0% [IQR 63.2–88.4] and 75.9% [53.6–100.6], respectively, with the best adequacy seen on day 5.

3.4. Hospital discharge with (par)enteral nutrition

Ten patients were discharged from the hospital with (supplemental) EN and one with supplemental PN. This patient group reached overall energy and protein adequacies above 95% during their post-ICU ward stay, as shown in Table 5.

3.5. Subgroup analyses: overall protein adequacy <90% and >90%

Subgroup analyses were performed based on achievement of less or more than 90% of protein targets (Table 6). The low intake (<90%) group had statistically significant higher mean SOFA (8.1 (SD 1.5) versus 5.2 (SD 2.3), $p = 0.001$) and NUTRIC scores (5.5 (SD 1.5) versus 4.5 (SD 1.2), $p = 0.022$) compared to the high intake group (>90% of targets reached). Of note, all patients who were discharged with (supplemental) (par)enteral nutrition achieved >90% of protein targets during their ward stay.

3.6. Secondary outcomes

An overview of discharge destinations, in-hospital-, 3- and 6-month mortality rates, readmission to ICU and hospital, length of ICU and hospital stay, and differences in MRC and CPax scores for low and high protein intake groups are summarised in Table 7.

No differences between groups were observed for any parameter (all $p > 0.05$).

The composite endpoint for unfavourable outcome (6-month hospital readmission or 6-month mortality) showed a positive trend for the high intake group, although this difference was not statistically significant ($p = 0.097$). This trend disappeared in univariable and multivariable COX regression with covariates gender, BMI and NUTRIC score (all $p > 0.05$).

Table 3

Nutritional data - patients with ORAL nutrition ONLY ($n = 11$).

A. All patients with ORAL nutrition only ($n = 11$).		Target	Ordered	p-value ^a	Intake	p-value ^a	Adequacy (%)
Energy (kcal/kg IBW*day)	median [IQR]	28.2 [26.8–30.6]	26.3 [25.1–31.2]	0.646	22.3 [18.8–29.3]	0.037*	82.2 [66.4–100.0]
Protein (g/kg IBW*day)	median [IQR]	1.36 [1.23–1.49]	1.27 [1.16–1.43]	0.285	1.07 [0.90–1.35]	0.093	75.5 [69.1–94.7]
B. Patients with energy and/or protein adequacy <90%		Target	Ordered	p-value ^a	Intake	p-value ^a	Adequacy (%)
Energy (kcal/kg IBW*day) ($n = 7$)	median [IQR]	28.1 [26.3–29.4]	25.4 [23.8–26.2]	0.018*	19.7 [17.9–22.1]	0.018*	70.1 [63.0–81.2]
Protein (g/kg IBW*day) ($n = 8$)	median [IQR]	1.33 [1.23–1.50]	1.17 [1.15–1.27]	0.018*	0.92 [0.84–1.13]	0.018*	73.8 [68.2–76.4]

Legend. IBW = ideal bodyweight; IQR = InterQuartile Range.

^a p-values were calculated using the one sample t-test and sign test where applicable (after calculating deficits in nutritional orders and intake compared to target).

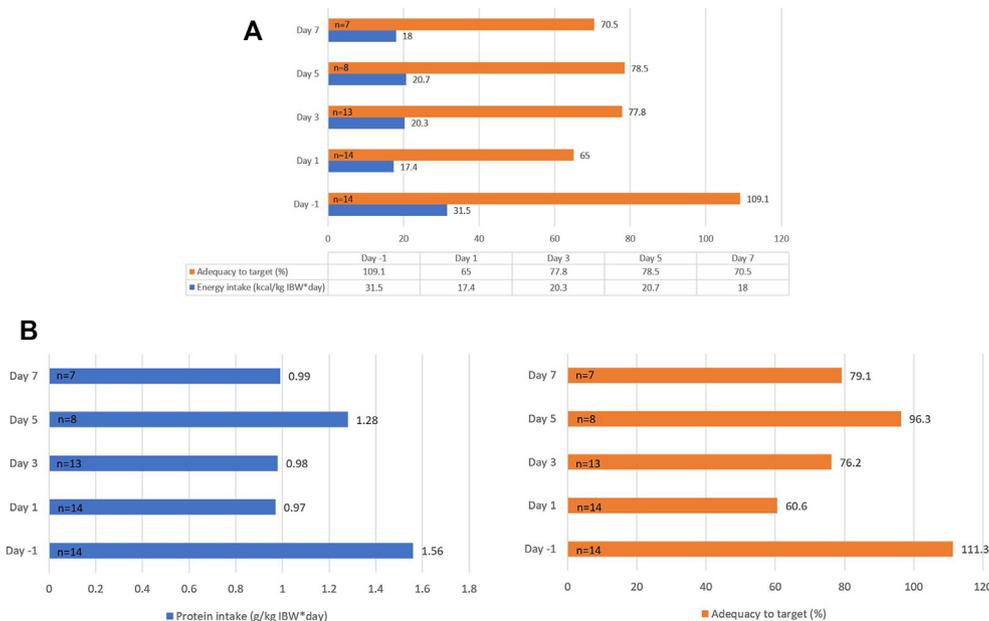


Fig. 2. Discontinuation of enteral nutrition in the post-Intensive Care Unit hospitalization period. Legend: day -1 = day before discontinuation; day 1 = first day after discontinuation; IBW = ideal bodyweight.

4. Discussion

The primary finding of this study is that energy and protein intake among post-ICU patients in general wards is below recommended and prescribed targets, due to insufficient (additional) oral intake. Mean overall energy and protein intake for all nutritional groups was 24.7 kcal/kg IBW*day and 1.25 g/kg IBW*day, corresponding to 82% and 83% of targets, respectively. Only 51.2% of prescribed protein targets during their post-ICU ward stay.

The observed adequacies are slightly higher than those reported in current literature. Chapple et al. reported energy and protein adequacies of 81% and 77% respectively, although their study population comprised 37 patients with moderate traumatic brain injury and not general ICU patients [17]. Ridley et al. conducted a nested cohort study within a randomized controlled trial (RCT) comparing supplemental PN with standard care, studying nutritional intake of 32 patients in the post-ICU hospitalization period [15]. They reported median overall energy and protein adequacies of 79% and 73%. Moisey et al. observed lower intakes, assessing nutritional intake in 19 patients during the first week after extubation [16]. They found overall median adequacies of energy and protein intake of 71% and 46%, respectively. Wittholz et al. who studied nutritional intake of multi-trauma patients during the first 5 days after ICU discharge, reported adequacies of 64% and 72% for energy and protein intake, respectively [23]. These reported adequacies might be lower than in our study because oral intake was the predominant nutritional mode during the study period (Ridley 55%, and Moisey 43% of study days versus 45% in our study). Moreover, differences in target calculations, assessment of nutritional intake (food record charts and patients recall) and days studied (second daily by Ridley et al., and immediately after extubation up to 8 days by Moisey et al.) may have further contributed to these differences. All studies consistently demonstrate that protein and energy targets are not reached after ICU-discharge.

Importantly, adequacy was highly dependent on patients' nutritional route. Patients with oral nutrition only had the lowest intake as overall adequacies of 82.2% and 75.5% for energy and

protein intake, were observed. Of note, these patients all received food fortification (energy/protein enriched) and/or ONS. In the aforementioned studies, patients only met up to 66% and 60% of prescribed energy and protein targets [15,16]. When no oral supplements were provided, energy and protein adequacies were notably worse: 37% and 48%, respectively [15].

Two other studies investigating oral intake post-extubation support these findings and demonstrate that energy and protein intake are below prescribed targets in patients with oral nutrition only after EN discontinuation [18,24].

Clinicians should consider that the prescribed calories and proteins are neither ordered nor consumed. Even the amount of food ordered was inadequate compared to targets. In patients failing to meet protein prescriptions (adequacy <90%), we found that the amount of protein ordered was statistically significant less than prescribed (median 1.17 versus 1.33 g/kg IBW*day; p = 0.018). In addition to this, prescriptions were below recommended protein intakes of at least 1.5 g/kg*day [7,8]. Similar findings were reported by Mitchell et al., who demonstrated that neither prescriptions nor delivery of EN met targets in the post-ICU hospitalization period [25].

In contrast, the best energy and protein adequacies ($\geq 95\%$) were observed among patients receiving (supplemental) (par)enteral nutrition until hospital discharge; none of these patients had an overall adequacy of <90% in our study. This is concordant with findings reported by Ridley et al., who demonstrated adequacies of 104% and 99% for energy and protein targets, respectively, in patients receiving supplemental EN [15]. However, not all of these EN patients reached their targets. Also, Chapple et al. reported energy and protein adequacies of 89% and 76% in patients receiving exclusive EN [17].

In most cases (81.3%), EN was terminated due to (supposed) sufficient energy and protein intake. However, 38.5% of these patients had an overall median protein adequacy of <90% before discontinuation. After EN discontinuation, the most significant drop in intake was seen during the first day. Subsequently, patients needed at least five days to reach a maximum adequacy at day 6 (median 75.2% and 103.2%, respectively), for energy and protein

Table 4
Nutritional data - transition from enteral feeding to oral nutrition ONLY during ward stay (n = 16).

A) Overview (n = 16)											
Duration of (supplemental) EN (full days)	median [IQR]		3 [1-5]								
Full observational days after stop EN	median [IQR]		6 [4-12]								
Energy target in ward (kcal/kg IBW*day)	median [IQR]		26.8 [25.9-29.0]								
Protein target in ward (g/kg*day)	N (%)										
1,2 g/kg*day			0 (0)								
1,2-1,5 g/kg*day			6 (37.5)								
1,5 g/kg*day			10 (62.5)								
Reason to stop EN	N (%)										
Accidental removal of FT			2 (12.5)								
Sufficient intake			13 (81.3)								
Patient refusal/complaints			1 (6.3)								
B) All observational days averaged (n = 16)											
		Before stop EN	After stop EN	p-value*							
Energy intake	median [IQR]										
Ordered (kcal/kg IBW*day)		13.5 [6.5-24.8]	23.6 [18.8-29.9]	0.008**							
Adequacy to target (%)		44.0 [23.5-89.8]	81.8 [69.8-109.2]	0.008**							
Intake (kcal/kg IBW*day)		27.6 [19.3-33.7]	20.9 [17.7-31.0]	0.441							
Contribution EN (%)		52.7 [46.4-83.7]	NA	NA							
Adequacy to target (%)		97.3 [77.3-119.8]	76.0 [63.0-88.9]	0.463							
Protein intake	median [IQR]										
Ordered (g/kg IBW*day)		0.62 [0.23-1.14]	1.37 [0.94-1.61]	0.008**							
Adequacy to target (%)		41.5 [18.8-79.1]	90.4 [62.9-116.5]	0.008**							
Intake (g/kg IBW*day)		1.27 [0.94-1.79]	1.12 [0.82-1.60]	0.374							
Contribution EN (%)		60.7 [48.0-87.7]	NA	NA							
Adequacy to target (%)		91.5 [78.0-142.4]	75.4 [55.2-101.7]	0.075							
C) Comparisons between observational days											
	Day -1	Day 1	p-value*	Day 3	p-value*	Day 5	p-value*	Day 6	p-value*	Day 7	p-value*
	(n=14)	(n=14)		(n=13)		(n=8)		(n = 7)		(n=7)	
Energy	median [IQR]	31.5 [24.8-37.4]	0.018**	20.3 [14.0-28.5]	0.046**	20.7 [19.4-38.9]	0.273	22.3 [16.5-28.4]	0.068	18.0 [13.3-21.0]	0.068
Adequacy		109.1 [85.1-139.7]	0.004**	77.8 [56.0-108.8]	0.248	78.5 [71.9-129.8]	0.273	75.2 [57.0-112.2]	0.249	70.5 [45.1-83.1]	0.116
Protein	median [IQR]	1.56 [1.22-2.02]	0.028**	0.98 [0.62-1.45]	0.046**	1.28 [0.76-1.80]	0.273	1.36 [0.66-1.64]	0.465	0.99 [0.67-1.40]	0.144
Adequacy		111.3 [78.2-149.6]	0.012**	76.2 [47.4-109.4]	0.062	96.3 [53.4-118.0]	0.273	103.2 [44.1-118.6]	0.463	79.1 [46.0-101.4]	0.173

Legend. Day 0 = stop EN.

EN = enteral nutrition; IBW = ideal bodyweight; FT = feeding tube.

** p-value <0.05.

Energy intake in kcal/kg IBW*day.

Protein intake in g/kg IBW*day.

Adequacy = adequacy to target (%).

*p-values were calculated using the Wilcoxon signed rank test; observational days were compared to day -1 (=day before discontinuation of EN).

Table 5
Nutritional data - patients with enteral nutrition until hospital discharge (n = 10).

Energy target in ward (kcal/kg*day)	median [IQR]	27.3 [26.2-29.0]
Energy intake, overall		
Ordered (kcal/kg IBW*day) (n = 7)		11.5 [4.5-22.6]
Intake (kcal/kg IBW*day)		26.3 [24.8-31.1]
Contribution EN (%)		89.8 [63.1-100]
Adequacy to target (%)		98.2 [94.2-100]
Protein target in ward (g/kg*day)	N (%)	
1,2 g/kg*day		1 (10)
1,2-1,5 g/kg*day		2 (20)
1,5 g/kg*day		7 (70)
Protein intake, overall	median [IQR]	
Ordered (g/kg IBW*day) (n = 7)		0.47 [0.22-1.16]
Intake (g/kg IBW*day)		1.50 [1.40-1.63]
Contribution EN (%)		92.4 [63.9-100]
Adequacy to target (%)		100 [98.1-100]

Legend. EN = enteral nutrition; IBW = ideal bodyweight; N = number; IQR = InterQuartile Range.

Adequacy was reported at a maximum of 100%.

targets. After discontinuation of EN, the amounts of energy and proteins ordered by patients increased significantly, although this was still not enough to reach prescribed targets (median adequacy to energy and protein targets: 81.8% and 90.4%, respectively).

We noticed a sustaining second drop in intake at day 7 after cessation of EN to energy and protein adequacies of 70.5% and 79.1%, although few patients (n = 7) were analyzed (as shown in Supplement 6). We hypothesize this is a result of discharge from the hospital of patients with the best adequacies (one patient with a protein adequacy of 111.7% in our study) or losing attention concerning adequate nutritional intake during the post-ICU hospitalization period.

Regarding secondary outcomes, no statistically significant clinical difference was found between patients reaching less or more than 90% of prescribed protein targets. This lack of significance might be due to underpowerment as inclusions had to be stopped prematurely due to the COVID-19 pandemic. Weijs et al. studying 801 patients surviving the post-ICU hospitalization period,

Table 6
Patients with overall <90% and >90% protein adequacy (all nutritional routes).

		Overall protein adequacy		p-value ^a
		<90%	>90%	
		(n=20)	(n=21)	
Age (years)	median [IQR]	75 [68–81]	72 [61–79]	0.411
Gender (male)	N (%)	13 (65)	6 (28.6)	0.019*
Type of admission (non-surgical)	N (%)	11 (55)	12 (57.1)	0.890
BMI on ICU admission (kg/m ²)	mean (SD)	28.0 (6.0)	25.4 (5.7)	0.158
APACHE II score on ICU admission	mean (SD)	21.9 (7.4)	19.0 (5.7)	0.179
SOFA score on ICU admission	mean (SD)	8.1 (1.5)	5.2 (2.3)	0.001*
SAPS II score	mean (SD)	45.1 (13.5)	41.4 (13.4)	0.538
NUTRIC score	mean (SD)	5.5 (1.5)	4.5 (1.2)	0.022*
Nutritional route at ICU discharge	N (%)			0.376
ORAL only		8 (40)	3 (14.3)	
ORAL + EN		6 (30)	8 (38.1)	
EN only		5 (25)	8 (38.1)	
PN ± EN ± ORAL		1 (5)	2 (9.6)	
Nutritional route at hospital discharge	N (%)			0.006*
ORAL only		19 (95)	9 (42.9)	
ORAL + EN		0 (0)	7 (33.3)	
EN only		0 (0)	3 (14.1)	
PN ± EN ± ORAL		0 (0)	1 (4.8)	
Not appropriate (moribund)		1 (5)	1 (4.8)	
Energy target in ward (kcal/kg IBW*day)	mean (SD)	28.0 (2.1)	28.7 (3.8)	0.948
Energy intake (kcal/kg IBW*day)	mean (SD)	19.3 (4.7)	29.7 (6.1)	<0.001*
Adequacy to target (%)		68.6 (16.2)	104.2 (20.1)	<0.001*
Protein target in ward (g/kg*day)	N (%)			0.713
1,2 g/kg*day		2 (10)	3 (14.3)	
1,2-1,5 g/kg*day		5 (25)	7 (33.3)	
1,5 g/kg*day		13 (65)	11 (52.4)	
Protein intake (g/kg IBW*day)	mean (SD)	0.93 (0.21)	1.55 (0.22)	<0.001*
Adequacy to target (%)		65.0 (14.9)	109.9 (13.6)	<0.001*

Legend. BMI = Body Mass Index; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; SAPS II = Simplified Acute Physiology Score; NUTRIC = Nutrition Risk in Critically ill; ICU = Intensive Care Unit; ORAL = oral nutrition; EN = enteral nutrition; PN = parenteral nutrition; IBW = ideal bodyweight; IQR = InterQuartile Range; N = number; SD = Standard Deviation.

*p-value <0.05.

^a p-values were calculated using Chi Square test, Fisher Exact test, two sample T-test or Mann–Whitney U test where appropriate.

demonstrated a decrease in 90-day mortality rate after hospital discharge with 17% for each 1 g/kg*day increase in protein intake [26]. A multicenter trial by Schuetz et al. and multiple single-day audits of food intake during NutritionDay outside critical care emphasize these results. These studies demonstrated a better 30-day survival in patients with increased energy and protein intakes [19,27,28]. We found no difference in global muscle strength (MRC score) between patients reaching 90% of protein targets or not, probably as this parameter has a ceiling effect, not being able to distinguish changes in patients with the highest scores.

4.1. Strengths

This study reports the most extensive and detailed observational data regarding meal consumption of post-ICU patients during their entire hospitalization period. We analyzed nearly 500 observational days using more than 1600 pictures and over 6500 meal order lines. Due to our hospital's meal order system, we were able to precisely quantify the number of kilocalories and grams of proteins ordered. All post-ICU hospitalization days were assessed until hospital discharge. Intake was measured daily (and before and after discontinuation of EN) in contrast with other studies [15–17]. Furthermore, all data on in-between meals ordered were recorded, not available in other studies [17]. Recall bias was eliminated as oral nutrition was objectively quantified through pre- and post-meal pictures, and assessed by two researchers independently after completing study participation [15,18]. Inter-rater agreement was excellent (ICC 0.878), partly because 2330 food order lines (35.1%) were graded 0 (not consumed), 1 (entirely consumed) or missing.

4.2. Limitations

Our study is limited by its single-center design and relatively small sample size. We aimed to include a larger sample, but inclusions had to be stopped prematurely due to the COVID-19 pandemic in March 2020. We might have introduced participants' bias among patients with oral nutrition. Patients were aware that their intake was measured daily. Moreover, the digital photography method has not been validated yet for non-trained observers. Only one study in a clinical setting has shown that the pre-post-meal picture method is valid and accurate compared with weighed food records in monitoring food intake in general wards [20]. Additionally, the picture method is labour-intensive and has some disadvantages and limitations. Due to technical problems with the cameras, the nutritional assessment of five patients could not be performed. In 7 patients only a few days could be analyzed due to missing pictures or bad quality. Products such as jelly, sugar, soups and ONS were difficult to analyze due to their opaque packaging. Not infrequently, packages from ordered products were missing in the post-meal photos, resulting in missing data which had to be extrapolated using less reliable methods.

We hypothesize that actual intake might be considerably lower than reported as details regarding food consumption by family members or thrown away before taking pictures was not considered. Moreover, due to poor registration, we could not collect data about gastric residual volumes and interruptions of (par)enteral nutrition in case of fasting for procedures or accidental feeding tube loss. This may contribute to nutritional shortfalls [17]. Conversely, we were unable to retrieve food record charts that reported food

Table 7
Outcome parameters.

		Overall protein adequacy			p-value ^b
		All patients	<90%	>90%	
		(n=41)	(n=20)	(n=21)	
Mortality	N (%)				
Hospital		2 (4.9)	1 (5)	1 (4.8)	0.972
3 months		6 (14.6)	4 (20)	2 (9.5)	0.410
6 months		7 (17.1)	5 (25)	2 (9.5)	0.238
Readmission to ICU (during hospital stay)	N (%)	3 (7.3)	1 (5)	2 (9.5)	0.578
Hospital readmission (yes)	N (%)	13 (31.7)	6 (30)	7 (33.3)	0.819
Within 3 months		8 (19.5)	4 (20)	4 (19.0)	
Within 6 months		10 (24.4)	6 (30)	4 (19.0)	
Within 12 months		13 (31.7)	6 (30)	7 (33.3)	
Composite endpoint mortality/HOS readmission ^a	N (%)	16 (39.0)	10 (50)	6 (28.6)	0.097
Length of stay (days)	median [IQR]				
ICU		9 [5–22]	10 [5–12]	9 [6–27]	0.478
Hospital (after ICU discharge)		12 [8–15]	10 [7–14]	12 [8–15]	0.289
Discharged from hospital with FT/CVC (yes)	N (%)	11 (26.8)	0 (0)	11 (50)	0.002*
Discharge destination	N (%)				0.706
Home		18 (43.9)	10 (50)	8 (38.1)	
Revalidation		21 (51.2)	9 (45)	11 (52.4)	
Psychiatric unit		1 (2.4)	0 (0)	1 (4.8)	
Mortuary		2 (4.9)	1 (5)	1 (4.8)	
MRC score at ICU discharge	median [IQR]	45 [37–48]	47 [39–48]	42 [36–48]	0.402
MRC score at HOS discharge	median [IQR]	48 [46–5]	48 [48–52]	48 [45–50]	0.496
Difference MRC score (HOS - ICU discharge)	median [IQR]	3 [0–6]	2 [0–6]	4 [0–8]	0.264
CPAx score at ICU discharge	median [IQR]	33 [24–39]	35 [20–40]	32 [24–39]	0.282
CPAx score at HOS discharge	median [IQR]	42 [38–46]	42 [40–45]	42 [37–46]	0.830
Difference CPax score (hospital - ICU discharge)	median [IQR]	7 [4–12]	7 [4–10]	7 [4–12]	0.977

Legend. ICU = Intensive Care Unit; HOS = hospital; FT = feeding tube; CVC = central venous catheter; MRC = Medical Research Council; CPax = Chelsea Critical Care Physical Assessment tool.

*p-value <0.05.

^a Composite endpoint composed of 6-month hospital readmission or 6-month mortality.

^b p-values were calculated using Chi Square test, Fisher Exact test, two sample T-test or Mann–Whitney U test where appropriate.

not registered, such as food brought in by family members. Finally, nutritional intake is expressed as study population based averages or medians. Patients with the highest adequacies may conceal the real nutritional intakes of patients with the lowest intakes (Supplement 4).

4.3. Future directions

We recommend further studies to extend individualized nutritional support to reach energy and protein targets in the post-ICU period. In the EFFORT multicenter RCT, studying 2088 general ward patients at risk for malnutrition, a beneficial effect of individualized nutritional support has been shown [19]. Therefore, we suggest monitoring intake (from all nutritional routes) daily and only stop EN when oral intake has proven to be sufficient, as recommended by Ridley et al. [14]. Subsequently, intake should be supported with food fortification or ONS, possibly even for a prolonged time after hospital discharge to facilitate recovery [10,12,14]. When targets are not reached after cessation of EN, reintroduction of EN should be considered in selected cases. Moreover, the importance of ordering and consuming adequate amounts of energy including proteins should be emphasized.

5. Conclusion

Most patients recovering from critical illness did not reach energy and protein targets during the post-ICU hospitalization period. However, this was highly dependent on the nutritional route, and was lowest among patients with oral nutrition only (despite of food fortification strategies and/or ONS). Additionally, the ordered amount of food failed to meet the predicted targets. Conversely, the best intake was seen in patients with (supplemental) EN; all these

patients reached adequacies >90%. Nonetheless, discontinuation of EN posed a nutritional risk, resulting in immediate and sustained drops of energy and protein intake. Patients needed an additional six days to increase intake to meet protein targets again. These findings highlight the need for follow-up studies to close the gap with individualized nutritional support in the post-ICU period. No statistically significant differences in clinical outcomes were observed in this study.

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Author contributions

Study design and concept: HSB, IvdH, ARHvZ.

Data collection: HSB, NS, LD, SM.

Statistical analysis and interpretation of data: HSB, MRM, ARHvZ.

Manuscript draft: HSB.

Critical revision of the manuscript: IvdH, NS, LD, SM, MRM, ARHvZ.

Conflict of interest

Prof. Dr A.R.H. van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from Baxter, Braun, Cardinal Health, Danone-Nutricia, Dim-3, Fresenius Kabi, Mermaid, Lyric, and Nestle-Novartis. The other authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2022.07.031>.

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