ORIGINAL ARTICLE

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

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ABSTRACT

BACKGROUND

The appropriate caloric goal for critically ill adults is unclear. We evaluated the effect of restriction of nonprotein calories (permissive underfeeding), as compared with standard enteral feeding, on 90-day mortality among critically ill adults, with maintenance of the full recommended amount of protein in both groups.

METHODS

At seven centers, we randomly assigned 894 critically ill adults with a medical, surgical, or trauma admission category to permissive underfeeding (40 to 60% of calculated caloric requirements) or standard enteral feeding (70 to 100%) for up to 14 days while maintaining a similar protein intake in the two groups. The primary outcome was 90-day mortality.

RESULTS

Baseline characteristics were similar in the two groups; 96.8% of the patients were receiving mechanical ventilation. During the intervention period, the permissive-underfeeding group received fewer mean (±SD) calories than did the standard-feeding group (835±297 kcal per day vs. 1299±467 kcal per day, P<0.001; 46±14% vs. 71±22% of caloric requirements, P<0.001). Protein intake was similar in the two groups (57±24 g per day and 59±25 g per day, respectively; P=0.29). The 90-day mortality was similar: 121 of 445 patients (27.2%) in the permissive-underfeeding group and 127 of 440 patients (28.9%) in the standard-feeding group died (relative risk with permissive underfeeding, 0.94; 95% confidence interval [CI], 0.76 to 1.16; P=0.58). No serious adverse events were reported; there were no significant between-group differences with respect to feeding intolerance, diarrhea, infections acquired in the intensive care unit (ICU), or ICU or hospital length of stay.

CONCLUSIONS

Enteral feeding to deliver a moderate amount of nonprotein calories to critically ill adults was not associated with lower mortality than that associated with planned delivery of a full amount of nonprotein calories. (Funded by the King Abdullah International Medical Research Center; PermiT Current Controlled Trials number, ISRCTN68144998.)

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Nutritional support is an essential component of the care of critically ill adults.[1] Achieving caloric targets has been recommended with the premise that attenuating malnutrition and protein catabolism, which are associated with increased morbidity and mortality, will improve outcomes.[2] Observational studies examining various doses of enteral feeding have yielded conflicting results.[3-7] Two cluster-randomized, controlled trials comparing higher enteral nutritional delivery with usual care in critically ill patients showed no reduction in mortality with the higher enteral nutrition.[8,9] Augmenting energy intake with early parenteral nutrition has been shown to result in no change in mortality[10] and in an increased time to discharge from the intensive care unit (ICU).[11]

Conversely, caloric restriction may be beneficial; it has been shown to prolong life span in several species,[12-14] promote mammalian cell survival,[15] and improve longevity biomarkers in humans,[16] possibly through its effects on metabolic, hormonal, and inflammatory pathways.[12,14,16] Among critically ill patients receiving parenteral nutrition, lower morbidity was observed with hypocaloric nutrition than with standard nutritional support.[17,18] Two randomized, controlled trials involving patients with acute lung injury or acute respiratory failure evaluated minimal or trophic enteral feeding (15 to 25% of estimated caloric requirements) with no protein supplementation for up to 6 days and showed outcomes that were similar to those with standard enteral feeding.[19,20] Whether restricting nonprotein calories (permissive underfeeding) in conjunction with meeting full protein requirements improves outcomes is unclear, although reviews of the existing evidence recommend a level of protein intake during early critical illness that is sufficient to satisfy full protein requirements,[21] regardless of the simultaneous caloric intake.[22] A study in rats showed that protein refeeding, but not glucose refeeding, restores mitochondrial function that has been reduced by malnutrition.[23] Therefore, it has been suggested that caloric restriction may be beneficial only if adequate dietary protein is provided.[24]

Such findings prompt the question of whether moderate caloric restriction while protein intake is preserved would improve the outcomes in critically ill adults. In a single-center, randomized, controlled trial of moderate caloric intake (60 to 70% of the estimated caloric requirement) versus standard caloric intake (90 to 100%), with maintenance of the full targeted protein intake in both groups, we observed that the lower caloric intake was associated with a reduction in in-hospital mortality, which was a secondary end point.[25] We hypothesized that a permissive-underfeeding strategy that restricts nonprotein calories but preserves protein intake, as compared with a standard feeding strategy, would reduce 90-day mortality among critically ill adults.

Methods

Study Design

The Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients (PermiT) trial was an unblinded, pragmatic, randomized, controlled trial conducted at seven tertiary care centers in Saudi Arabia and Canada between November 2009 and September 2014. The institutional review board at each participating center approved the study. Written informed consent was obtained from all the patients or their legal representatives. The study was sponsored by the King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, and the investigators designed, managed, and analyzed the study independently. Patients were eligible for the trial if they were fed enterally within 48 hours after ICU admission. Inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The study protocol is also available at NEJM.org.

Interventions

Enrolled patients were randomly assigned to the permissive-underfeeding group or the standard-feeding group with the use of opaque, sealed, sequentially numbered envelopes. The randomization list was computer-generated. Randomization was performed in random permuted blocks and was stratified according to center. The feeding strategy was unblinded because of the need for adjustment of the nutritional support according to feeding tolerance and gastric residual volumes. ICU dietitians estimated patients' standard caloric requirements using the equation developed by investigators at Pennsylvania State

University (the Penn State equation) for mechanically ventilated patients who had a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of less than 30 and using the 1992 Ireton-Jones equation for mechanically ventilated patients who had a BMI of 30 or higher and for spontaneously breathing patients (Table S2 in the Supplementary Appendix).[26-28]

The caloric goal was 40 to 60% of caloric requirements in the permissive-underfeeding group and 70 to 100% of caloric requirements in the standard-feeding group. We set the caloric goal in the permissive-underfeeding group at a lower level than we did in the earlier trial,[25] with the premise that a larger separation in caloric intake between the two groups would lead to a larger treatment effect. The assigned intervention was continued for up to 14 days or until ICU discharge, initiation of oral feeding, death, or withholding of nutrition as part of palliation. Participating centers used their own protocols to guide delivery of enteral feeding. Daily caloric targets were established to achieve the prescribed nutritional delivery, and if caloric intake was below the target on a given day, intake was increased the following day to compensate. Calculation of actual intake included calories received from propofol, intravenous dextrose, and parenteral nutrition. Additional details of the interventions have been published previously[29] and are also provided in the Supplementary Appendix.

COINTERVENTIONS

Protein requirements were calculated at 1.2 to 1.5 g per kilogram of body weight per day, in accordance with clinical practice guidelines.[1] To ensure that enteral protein and volume delivery in the permissive-underfeeding group would be similar to those in the standard-feeding group, the permissive-underfeeding group received additional protein (Beneprotein, Nestlé Nutrition) and normal saline or water at a dose of 2 ml per kilogram every 4 hours unless otherwise specified by the clinical team.[25] The study protocol provided suggestions on the selection of enteral formulas on the basis of published guidelines[1]; however, the decision was left to the clinical team (Table S3 in the Supplementary Appendix). Study centers used their own insulin protocols, with a target blood glucose level of 4.4 to 10 mmol per liter (80 to 180 mg per deciliter) in both groups. The study protocol recommended daily enteral multivitamins for all patients (Table S4 in the Supplementary Appendix). All other cointerventions were left to the discretion of the treating team.

DATA COLLECTION

At baseline, we collected data on patient demographics, diabetes history, admission category (medical, surgical, or trauma), Acute Physiology and Chronic Health Evaluation (APACHE) II score,[30] Sequential Organ Failure Assessment (SOFA) score,[31] and use of mechanical ventilation, vasopressors, or renal-replacement therapy. We also measured levels of blood glucose, creatinine, bilirubin, hemoglobin, platelets, glycated hemoglobin, C-reactive protein, serum lipids (triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein), albumin, prealbumin, and transferrin. In addition, we assessed the international normalized ratio, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and 24-hour urinary nitrogen excretion.

Daily during the intervention period, we obtained nutritional data (total calories and calories from enteral feeding, propofol, intravenous dextrose, and parenteral nutrition), laboratory data (levels of blood glucose, hemoglobin, creatinine, potassium, magnesium, and phosphate), and information on insulin dose, fluid intake and output, use of prokinetic agents, stool frequency and consistency, and duration of interruption in feeding. On a weekly basis, we recorded body weight; levels of lipids, prealbumin, and transferrin; and 24-hour urinary nitrogen excretion. We also recorded the use of selected medications during the ICU stay. Information on the monitoring of serious adverse events is provided in Table S5 in the Supplementary Appendix.

OUTCOMES

The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality in the ICU, 28-day mortality, in-hospital mortality, 180-day mortality, and serial SOFA scores. Tertiary outcomes included days free from mechanical ventilation, ICU-free days, hospital length of stay, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusions of packed

red cells, ICU-associated infections (documented by the research coordinator according to published definitions[32]), feeding intolerance (vomiting, abdominal distention, or a gastric residual volume of more than 200 ml), and diarrhea.

STATISTICAL ANALYSIS

On the basis of the findings of our previous randomized, controlled trial,[25] we estimated that permissive underfeeding would be associated with an absolute risk reduction in mortality of 8 percentage points. Assuming an estimated 90-day mortality of 25% with standard feeding, we calculated that enrollment of 432 patients in each group would give the study 80% power to detect the 8-percentage-point difference in mortality. With an estimated 3% loss to follow-up, the final calculated sample size was 892 patients. The primary outcome was compared between the two groups with use of the chi-square test; the results were reported as relative risks and 95% confidence intervals. We performed an unadjusted Cox proportional-hazards analysis as well as an analysis adjusted for BMI, APACHE II score, and baseline vasopressor use, with the results reported as hazard ratios and 95% confidence intervals.

For serial measurements, we tested the change over time and the difference between the two groups over time using a repeated-measures analysis of variance, with no imputation for missing values. The primary outcome was compared between the two study groups in the following prespecified subgroups: nonsurgical patients versus surgical patients, patients with diabetes versus patients without diabetes, patients with an APACHE II score of 18 or lower versus those with a score higher than 18, patients with a specific admission diagnosis (severe sepsis or traumatic brain injury) versus patients without either of those diagnoses, patients using vasopressors at baseline versus those not using them, and patients with a blood glucose level of no more than the median value at randomization versus those with a level higher than the median value. Tests were two-sided and at the 5% significance level. For serial measurements, we used a Bonferroni correction to account for multiple comparisons. To account for alpha spending by the interim analyses, we used the O'Brien–Fleming method. A final P value of less than 0.045 was considered to indicate statistical significance for the primary outcome. Analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

A total of 894 patients underwent randomization (Fig. S1 in the Supplementary Appendix). At baseline, the two groups were similar with respect to demographic, physiological, and nutritional characteristics (Table 1, and Table S6 in the Supplementary Appendix). A total of 96.8% of the patients were receiving mechanical ventilation.

INTERVENTIONS AND COINTERVENTIONS

Throughout the intervention period, patients in the permissive-underfeeding group had a lower caloric intake than did patients in the standard-feeding group (Table 2 and Fig. 1, and Fig. S2 in the Supplementary Appendix); the average caloric intake during the intervention period was 46±14% versus 71±22% of daily requirements (P<0.001). Protein intake and the enteral formulas used did not differ significantly between the two groups (Table 2, and Table S7 and Fig. S3 in the Supplementary Appendix). Patients in the permissive-underfeeding group had lower glucose levels, required less insulin, and had lower daily fluid balance on several study days (Table 2 and Fig. 1). Other cointerventions and nutrition-related data are shown in Table 2 and Figure 1, and Figure S4 in the Supplementary Appendix.

OUTCOMES

Mortality

The 90-day mortality (primary end point) was 27.2% (121 of 445 patients) in the permissive-underfeeding group and 28.9% (127 of 440 patients) in the standard-feeding group (relative risk, 0.94; 95% confidence interval [CI], 0.76 to 1.16; P=0.58) (Table 3). Unadjusted and adjusted hazard ratios were also nonsignificant (unadjusted hazard ratio, 0.92; 95% CI, 0.72 to 1.18; P=0.51; adjusted hazard ratio, 0.91; 95% CI, 0.71 to 1.17; P=0.48). Similarly, there were no significant between-group differences with respect to mortality in the ICU, in-hospital mortality, 28-day mortality, or 180-day mortality. Kaplan–Meier survival estimates showed no significant differ-

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Variable	Permissive Underfeeding (N=448)	Standard Feeding (N=446)
Age — yr	50.2±19.5	50.9±19.4
Female sex — no. (%)	156 (34.8)	164 (36.8)
Body-mass index†	29.0±8.2	29.7±8.8
Diabetes — no. (%)	159 (35.5)	153 (34.3)
Admission category — no. (%)		
Medical	336 (75.0)	335 (75.1)
Surgical	19 (4.2)	12 (2.7)
Nonoperative trauma	93 (20.8)	99 (22.2)
Severe sepsis at admission — no. (%)	159 (35.5)	133 (29.8)
Traumatic brain injury — no. (%)	55 (12.3)	63 (14.1)
APACHE II score‡	21.0±7.9	21.0±8.2
SOFA score§	9.9±3.5	9.8±3.5
Mechanical ventilation — no. (%)	436 (97.3)	429 (96.2)
Vasopressor therapy — no. (%)	255 (56.9)	243 (54.5)
Glycated hemoglobin — mmol/liter	0.07±0.06	0.07±0.08
C-reactive protein — mg/liter	131±80	125±82
Serum lipid levels — mmol/liter		
Triglycerides	1.56±1.07	1.58±1.17
Total cholesterol	2.66±1.07	2.77±0.98
Low-density lipoprotein	1.29±0.78	1.34±0.72
High-density lipoprotein	0.59±0.33	0.64±0.40
Albumin — g/liter	28±7	28±6
Prealbumin — g/liter	0.15±0.13	0.14±0.12
Transferrin — g/liter	1.36±0.49	1.38±0.50
24-hour urinary nitrogen excretion — mmol	284±176	303±219
Time from eligibility to randomization — hr	8.3±11.6	7.9±12.3

* Plus–minus values are means ±SD. There were no significant between-group differences. Data on laboratory values were not available for some patients; the numbers of patients with available data in the permissive-underfeeding group and the standard-feeding group, respectively, were as follows: glycated hemoglobin, 268 patients and 284 patients; C-reactive protein, 357 patients and 360 patients; triglycerides, 375 patients and 376 patients; total cholesterol, 373 patients and 372 patients; low-density lipoprotein, 366 patients and 363 patients; high-density lipoprotein, 374 patients and 375 patients; prealbumin, 334 patients and 341 patients; transferrin, 359 patients and 361 patients; and 24-hour urinary nitrogen excretion, 305 patients and 292 patients.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease.
§ Scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure.

ence in the probability of survival between the two groups (P=0.43 by the log-rank test) (Fig. 2).

Other End Points

Serial SOFA scores, nitrogen balance, body weight, and levels of C-reactive protein, prealbumin, creatinine, bilirubin, partial pressure of arterial carbon dioxide, hemoglobin, lipids, potassium, magnesium, phosphate, transferrin, and urinary nitrogen excretion did not differ significantly between the two groups (Fig. 1, and Fig. S5 through S10 in the Supplementary Appendix). The number of days free from mechanical ventilation and the number of ICU-free

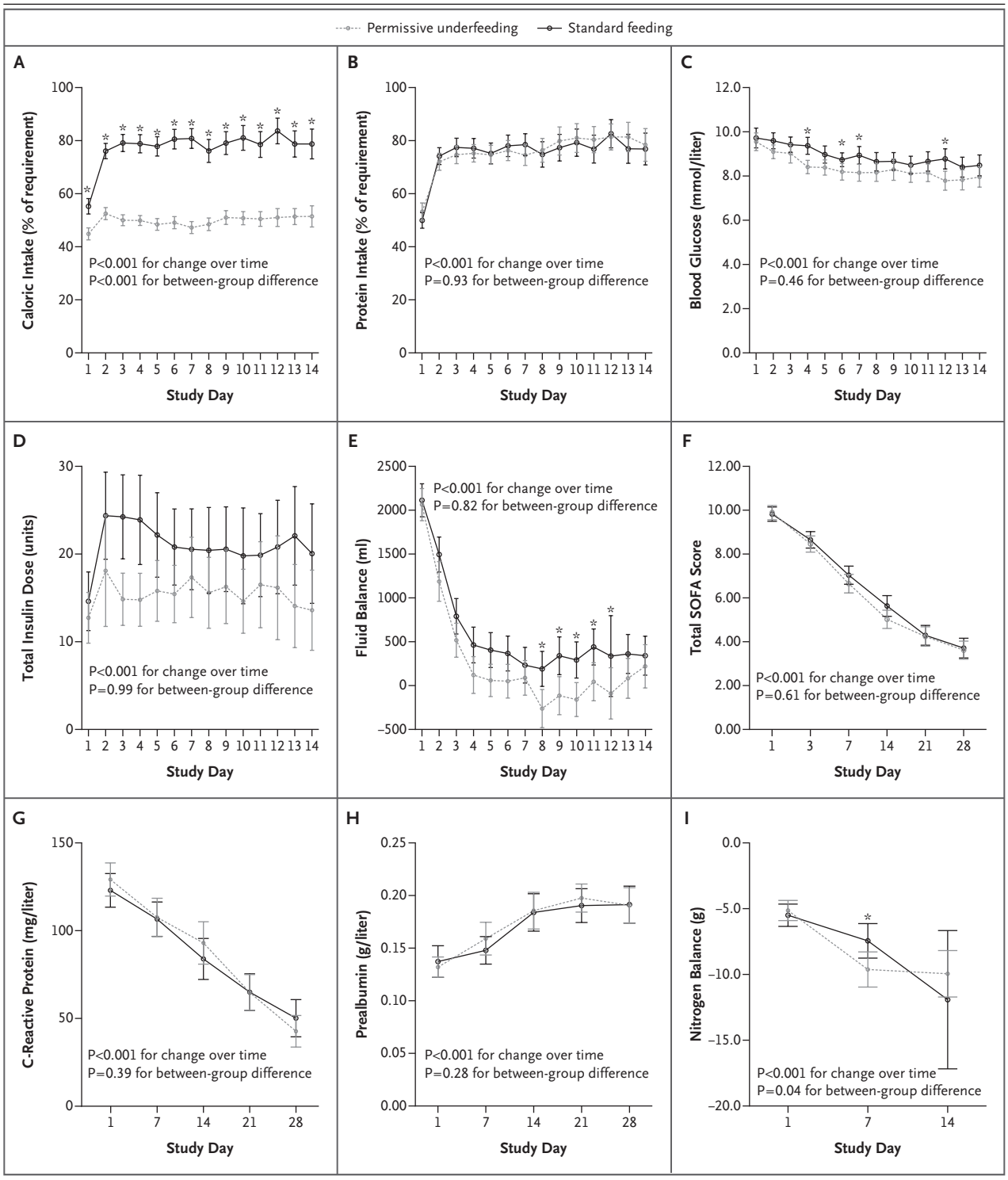
Table 2. Study Interventions and Cointerventions.*

Variable	Permissive Underfeeding (N=448)	Standard Feeding (N=446)	P Value
Calculated caloric requirement — kcal/day	1822±377	1842±370	0.51†
Caloric target for the trial — kcal/day	1036±262	1826±375	<0.001†
Daily caloric intake for duration of intervention			
No. of kilocalories	835±297	1299±467	<0.001‡
Percent of requirement	46±14	71±22	<0.001†
Caloric source for duration of intervention — kcal/day			
Enteral	740±294	1198±470	<0.001‡
Propofol	63±88	65±89	0.84†
Intravenous dextrose	32±59	35±60	0.23†
Parenteral nutrition	3±32	5±59	0.38†
Calculated protein requirement — g/day	85±21	88±23	0.18†
Daily protein intake for duration of intervention			
No. of grams	57±24	59±25	0.29†
Percent of requirement	68±24	69±25	0.56†
Protein source — g/day			
Main enteral formula	30±13	54±22	<0.001†
Supplemental enteral protein	27±16	6±10	<0.001†
Parenteral protein	0.2±2.6	0.2±2.7	0.79†
Duration of intervention — days	9.1±4.6	9.4±4.4	0.36†
Cointerventions during study period			
Insulin			
Use — no. (%)	205 (45.8)	235 (52.7)	0.04
Dose — units/day	15±27	22±40	0.02†
Enteral formulas on day 1 — no./total no. (%)§			
With a specific disease indication	263/441 (59.6)	240/443 (54.2)	0.10
Without a specific disease indication	178/441 (40.4)	203/443 (45.8)	
Prokinetics — no. (%)¶	120 (26.8)	127 (28.5)	0.57
Blood glucose — mmol/liter	9.1±5.3	9.4±5.0	0.04†
Fluid balance — ml/day	490±1408	688±1196	<0.001†

* Plus–minus values are means ±SD. To convert values for blood glucose to milligrams per deciliter, divide by 0.05551.
† P values were calculated with the use of the Wilcoxon–Mann–Whitney test.
‡ P values were calculated with the use of the independent Student's t-test.
§ Information on formulas with a specific disease indication and those without a specific disease indication is provided in Tables S3 and S7 in the Supplementary Appendix.
¶ Prokinetics included metoclopramide, erythromycin, domperidone, and any combination of these.

Figure 1 (facing page). Serial Measurements of the Intervention, Cointerventions, and Selected Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.

The values shown are means; I bars indicate 95% confidence intervals. Asterisks denote statistical significance, after Bonferroni correction, for the difference between the two groups on each day, with the use of the independent Student's t-test (for daily caloric intake) and Wilcoxon–Mann–Whitney test (for all other variables). P values for the change over time for both groups combined and for the difference between the two groups over time were calculated with the use of repeated-measures analysis of variance. Total scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. Nitrogen balance was calculated as [total protein intake in grams÷6.25]−[(urinary nitrogen excretion in millimoles÷35.7)+4 g]. To convert values for blood glucose to milligrams per deciliter, divide by 0.05551.



days did not differ significantly between the two groups (Table 3, and Table S8 in the Supplementary Appendix). In addition, there were no significant between-group differences with respect to hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, transfusion of packed red cells, ICU-acquired infections, diarrhea, or feeding intolerance. Post hoc analysis showed

Table 3. Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.*

Outcome	Permissive Underfeeding (N=448)	Standard Feeding (N=446)	Relative Risk (95% CI)	P Value
Death by 90 days — no./total no. (%)	121/445 (27.2)	127/440 (28.9)	0.94 (0.76–1.16)	0.58
Death in the ICU — no. (%)	72 (16.1)	85 (19.1)	0.84 (0.63–1.12)	0.24
Death by 28 days — no./total no. (%)	93/447 (20.8)	97/444 (21.8)	0.95 (0.74–1.23)	0.7
Death in the hospital — no./total no. (%)	108/447 (24.2)	123/445 (27.6)	0.87 (0.70–1.09)	0.24
Death by 180 days — no./total no. (%)	131/438 (29.9)	140/436 (32.1)	0.93 (0.76–1.14)	0.48
Duration of mechanical ventilation — days				
Median	9	10		0.49†
Interquartile range	5–15	5–16		
Days free from mechanical ventilation				
Median	77	75		0.48†
Interquartile range	0–84	0–84		
ICU length of stay — days				
Median	13	13		0.46†
Interquartile range	8–21	8–20		
ICU-free days				
Median	72	71		0.28†
Interquartile range	0–81	0–79		
Hospital length of stay — days				
Median	28	30		0.24†
Interquartile range	15–54	14–63		
Hypoglycemia — no. (%)	6 (1.3)	7 (1.6)	0.85 (0.29–2.52)	0.77
Hypokalemia — no. (%)	101 (22.5)	91 (20.4)	1.10 (0.86–1.42)	0.44
Hypomagnesemia — no. (%)	127 (28.3)	131 (29.4)	0.97 (0.79–1.19)	0.74
Hypophosphatemia — no. (%)	267 (59.6)	261 (58.5)	1.01 (0.91–1.14)	0.74
Transfusion of packed red cells — no. (%)	141 (31.5)	142 (31.8)	0.99 (0.82–1.20)	0.91
Incident renal-replacement therapy — no./total no. (%)	29/406 (7.1)	45/396 (11.4)	0.63 (0.40–0.98)	0.04
ICU-associated infection — no. (%)	161 (35.9)	169 (37.9)	0.95 (0.80–1.13)	0.54
Urinary tract infection — no. (%)	45 (10.0)	48 (10.8)	0.93 (0.64–1.37)	0.73
Catheter-related infection — no. (%)	11 (2.5)	19 (4.3)	0.58 (0.28–1.20)	0.13
Ventilator-associated pneumonia — no. (%)	81 (18.1)	90 (20.2)	0.90 (0.68–1.17)	0.43
ICU-associated severe sepsis or septic shock — no. (%)	61 (13.6)	58 (13.0)	1.05 (0.75–1.46)	0.79
Feeding intolerance — no. (%)	67 (15.0)	79 (17.7)	0.84 (0.63–1.14)	0.26
Diarrhea — no. (%)	97 (21.7)	117 (26.2)	0.83 (0.65–1.04)	0.11

* The number of days free from mechanical ventilation and the number of intensive care unit (ICU)–free days were calculated for the first 90 study days and were considered to be 0 for patients who died on or before day 90. Hypoglycemia was defined as a blood glucose level of less than 2.2 mmol per liter (40 mg per deciliter), hypokalemia as a potassium level of less than 2.8 mmol per liter, hypomagnesemia as a magnesium level of less than 0.60 mmol per liter, and hypophosphatemia as a phosphate level of less than 0.70 mmol per liter. Feeding intolerance was defined as vomiting, abdominal distention, or a gastric residual volume of more than 200 ml. Diarrhea was defined as three or more loose or liquid stools per day for 2 consecutive days.

† P values were calculated with the use of the Wilcoxon–Mann–Whitney test.

that incident renal-replacement therapy was required less frequently in the permissive-underfeeding group than in the standard-feeding group (29 of 406 patients [7.1%] vs. 45 of 396 patients [11.4%]; relative risk, 0.63; 95% CI, 0.40 to 0.98; P=0.04). No serious adverse events were reported.

Prespecified Subgroup Analyses

There were no significant differences in 90-day mortality between the two study groups in any of the prespecified subgroups (Table S9 in the Supplementary Appendix). Tests of interactions were not significant for any of the subgroups.

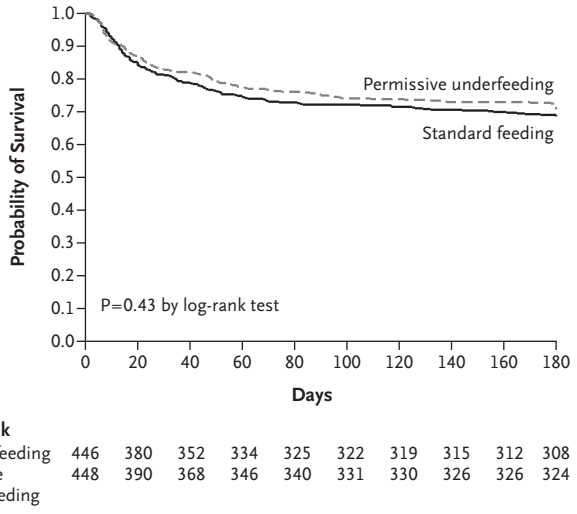


Figure 2. Kaplan–Meier Curves for Survival up to 180 Days after Enrollment.

DISCUSSION

In our study, a strategy of enteral feeding for critically ill adults in which patients received a moderate amount of nonprotein calories (40 to 60% of estimated caloric requirements), along with the full recommended amount of protein, had no significant effect on mortality, as compared with a strategy in which patients received 70 to 100% of estimated caloric requirements. These findings are similar to those of two previous randomized, controlled trials that evaluated minimal or trophic feeding (15 to 25% of caloric requirements for up to 6 days) in patients with acute lung injury or acute respiratory failure.[19,20]

Our trial has several important differences from the two earlier trials. First, the degree of caloric restriction in our trial was more moderate but the duration was more prolonged. Second, we administered supplemental protein in the permissive-underfeeding group, thus eliminating the confounding effect of differential and reduced protein intake. Third, we administered enteral normal saline or water to minimize the differences in delivered enteral volume, which may explain the lack of difference in the incidence of feeding intolerance between the study groups in our trial, a difference that was observed in the other two trials. Fourth, we estimated caloric requirements as total calories and not, as in the other two studies, as nonprotein calories. Although there is no evidence to support the superiority of our approach, we assumed that in the catabolic state of our severely ill patients, protein does contribute to energy requirements. Most commercial formulas list protein as a caloric component, accounting for 15 to 20% of calories (Table S3 in the Supplementary Appendix); therefore, not including calories from protein may lead to overfeeding.[33] Despite these differences, however, the collective results of our study and the two previous trials add to a growing body of research that suggests that standard feeding goals in critically ill patients do not improve clinical outcomes.

Permissive underfeeding was associated with lower blood glucose levels and reduced insulin requirements, findings that are consistent with those of other studies.[20,25] Our study does not support the premise that higher caloric intake attenuates protein catabolism in critically ill patients, because the two groups had similar clinical indexes of protein status, including nitrogen balance and levels of prealbumin, transferrin, and urinary nitrogen excretion. However, the limitations of these indexes in assessing protein status in ICU patients must be noted.[21] Prealbumin and transferrin levels are influenced by nonnutritional factors such as the level of inflammation, fluid status, and iron depletion. Nitrogen balance studies that are based on the measurement of urinary nitrogen excretion are subject to day-to-day variation and do not take into account nonurinary nitrogen losses such as those that occur as a result of diarrhea or fistulas.[21] We also found no significant between-group difference with respect to ICU-acquired infections, a finding that is consistent with the results of other studies.[19,20,25,34]

Could caloric intake matter in certain subpopulations? One randomized, controlled trial involving 82 patients with traumatic brain injury showed better 3-month neurologic outcomes with a higher caloric intake but no significant differences in 6-month outcomes or mortality.[35] Similarly, we found no effect of feeding strategy on mortality among 118 patients with traumatic brain injury. The lack of significance in tests of interaction suggests that permissive underfeeding, as compared with standard feeding, has no differential effect in prespecified subgroups. However, some of these subgroup analyses may have been underpowered owing to the small size of the subgroup.

The lower requirement for incident renal-replacement therapy in the permissive-underfeeding group was a finding in a post hoc analysis and should therefore be interpreted cautiously. However, our finding supports the notion that higher caloric intake may be associated with kidney injury. Caloric restriction has been shown to be renoprotective in animal models of acute kidney injury,[36-38] through several mechanisms, including improved insulin sensitivity.[38] In contrast to our study, previous randomized, controlled trials did not show significant differences in the rates of renal-replacement therapy or in the number of days free from renal failure between patients assigned to caloric restriction and those assigned to full caloric intake.[19,20,25] However, those studies varied in the degree and duration of caloric restriction,[28,29] and some may have been underpowered.[25,39] Reductions in the rate of acute renal impairment and in the rate of the need for renal-replacement therapy were reported with intensive insulin therapy as compared with standard insulin therapy,[40] which suggests that hyperglycemia may contribute to kidney injury. A higher fluid balance in the standard-feeding group may correlate with the observed higher requirement for renal-replacement therapy. Clinical practice guidelines recommend standard caloric and protein intake in patients with acute kidney injury and increasing protein intake during renal-replacement therapy,[1] but further research is required.

Strengths of this study include the multicenter design and the pragmatic inclusion of critically ill adults with a medical, surgical, or trauma admission category; these features increase the generalizability of the results. The inclusion of patients in whom enteral feeding was initiated early during critical illness avoided the confounding effect of the timing of feeding.

The study also had limitations. First, only 14% of the patients who were admitted to the ICU and screened were included in the study; therefore, the results may not be generalizable to other patients, such as those in whom enteral feeding was initiated late. Second, the target caloric intake was not reached in some patients, particularly in the standard-feeding group. This is not unusual in critically ill patients, given that feeding intolerance and feeding interruptions are common. Nevertheless, there was significant separation in caloric intake between the two groups. Third, blinding of the intervention was not possible, but important nutritional cointerventions were standardized and the primary outcome was objective. Fourth, the duration of intervention in our study was fixed; therefore, the effect of permissive underfeeding for a duration that is individualized on the basis of the critical illness remains to be studied. Fifth, we did not monitor adherence to multivitamin supplementation and did not have a formal adjudication process for the secondary outcome of infections. Finally, our study was powered to detect an absolute risk reduction of 8 percentage points in 90-day mortality; thus, we cannot rule out a smaller treatment effect.

In conclusion, a strategy of enteral feeding to provide a moderate amount of calories to critically ill adults in the presence of full protein intake was not associated with lower mortality than a strategy aimed at providing a full amount of calories.

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Permissive Underfeeding or Standard Enteral Feeding in High and Low Nutritional Risk Critically Ill Adults: Post-hoc Analysis of the PermiT trial

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At Glance Commentary
Scientific Knowledge on the Subject
Should nutritional support be different among critically ill patients based on their baseline nutritional status? There is a dearth of RCT data regarding the optimal nutritional strategy in patients at high nutritional risk.

What This Study Adds to the Field
Among patients with high and low nutritional risk, permissive underfeeding with full protein intake was associated with similar 90-day mortality as standard feeding. Neither the NUTRIC score nor other baseline nutritional variables could identify who may benefit from full caloric intake.

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Abstract

Rationale: The optimal nutritional strategy for critically ill adults at high nutritional risk is unclear.

Objective: In patients with different baseline nutritional risk, we examined the effect of permissive underfeeding with full protein intake compared to standard feeding on 90-day mortality.

Methods: This is a post-hoc analysis of the PermiT (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients) trial.

Measurements: Nutritional risk was categorized by the modified Nutrition Risk in Critically Ill (NUTRIC) score, with high nutritional risk defined as score 5-9 and low nutritional risk as score 0-4. Additional analyses were performed by categorizing patients by body mass index, prealbumin, transferrin, phosphate, urinary urea nitrogen and nitrogen balance.

Main Results: Based on the NUTRIC score, 378/894 (42.3%) patients were categorized as high nutritional risk and 516/894 (57.7%) as low nutritional risk. There was no association between feeding strategy and mortality in the two categories; adjusted-odds ratio (aOR) 0.84 (95% CI 0.56-1.27) for high nutritional risk and 1.01 (95% CI 0.64-1.61) for low nutritional risk (interaction p=0.53). Findings were similar in analyses using other definitions, with the exception of prealbumin. The association of permissive underfeeding versus standard feeding and 90-day mortality differed when patients were categorized by baseline prealbumin level (≤0.10 g/L: aOR 0.57 (0.31-1.05); >0.10 and ≤0.15 g/L: aOR 0.79 (0.42-1.48); >0.15 g/L aOR 1.55 (0.80, 3.01); interaction p=0.009).

Conclusions: Among patients with high and low nutritional risk, permissive underfeeding with full protein intake was associated with similar outcomes as standard feeding.

Key words: critical care, insulin, mortality, enteral nutrition, caloric intake, enteral feeding, permissive underfeeding, caloric restriction, infections, intensive care.

Introduction

Recent randomized controlled trials (RCTs) of restricted caloric intake compared with standard feeding showed no difference in mortality in critically ill patients.(1-3) However, it has been suggested that caloric intake should be targeted based on the underlying nutritional status. Observational studies have found that full caloric intake was associated with improved outcomes in critically ill adults at high nutritional risk.(4, 5) Conversely, other observational studies have suggested that malnourished patients are at high risk of refeeding syndrome with its adverse consequences, and thus recommend a restricted caloric strategy for these patients.(6) There is a dearth of RCT data regarding the optimal nutritional strategy in patients at high nutritional risk. Only one RCT has compared restricted versus standard caloric intake in critically ill patients with refeeding syndrome, defined as hypophosphatemia within 72 hours of initiation of nutrition.(7) While the number of days alive after ICU discharge did not differ between the two groups, caloric restriction was associated with more patients alive at day 60 and longer overall survival. However, whether these patients were at high nutritional risk is unclear, as the average body mass index (BMI) in the study population was 28 kg/m^2 and only 3% of patients had a BMI less than 18 kg/m^2. Therefore, the optimal caloric intake during critical illness in patients at high nutritional risk remains unclear.

A major challenge in tailoring nutrition in critically ill patients is the lack of consensus regarding the definition of nutritional risk.(8) The Nutrition Risk in Critically ill (NUTRIC) score has been proposed to quantify nutritional risk and identify critically ill patients most likely to benefit from aggressive nutrition therapy.(4) The score includes age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, number of co-morbidities, days from hospital admission to ICU admission and interleukin 6 (IL-6). A modified version of the NUTRIC score which excludes IL-6 has been validated in an observational study; the total score ranges from 0 to 9 with increasing scores indicating higher nutritional risk.(5) A strong association was found between nutritional adequacy and 28-day survival in patients with a high NUTRIC score; this association diminished with decreasing NUTRIC score.(5) Based on this finding, the NUTRIC score has been proposed to identify critically ill patients most likely to benefit from optimal amounts of macronutrients.(5, 8) Other commonly used measures of nutritional risk include BMI, prealbumin (also called transthyretin), transferrin, serum phosphate, urinary urea nitrogen (UUN) and nitrogen balance. With the exception of phosphate

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(7) the value of these measures in guiding nutritional support has not been examined in an RCT setting.(9-11)

The objective of this analysis was to examine the effect of permissive caloric underfeeding compared with standard feeding on 90-day mortality in critically ill adults stratified by baseline nutritional status, using the NUTRIC score and other common measures of nutritional risk.

Methods

Study Design

This was a post-hoc analysis of the PermiT trial (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients), an unblinded pragmatic RCT conducted in 7 tertiary-care centers in Saudi Arabia and Canada (ISRCTN Registry: ISRCTN68144998) between November 2009 and September 2014. The Institutional Review Boards of the participating centers approved the study, and informed consent was obtained from surrogate decision makers prior to enrollment. In this trial, 894 patients were randomized to permissive underfeeding (with a goal of 40-60% caloric requirement) or standard feeding (with a goal of 70-100% caloric requirement) with a goal of similar protein intake (1.2-1.5 g/kg/day) in both groups. Complete details of the study protocol and results have been previously published.(2, 12) The trial found no difference in the primary endpoint of 90-day mortality between the permissive and standard feeding groups (relative risk 0.94, 95% CI 0.76, 1.16; p=0.58).

Nutritional risk

We used the validated modified NUTRIC score to categorize patients as high nutritional risk if their score was 5-9, and low nutritional risk if their score was 0-4. We also categorized patients based on BMI (weight in kilograms divided by the square of the height in meters [kg/m^2]) measured on the day of ICU admission using the World Health Organization (WHO) criteria as underweight (<18.5 kg/m^2), normal weight (18.5–24.99 kg/m^2), overweight (25.0–29.99 kg/m^2), obese (30.0–40 kg/m^2) or very obese (>40 kg/m^2).(13) Patients were categorized based on the lower limit of the laboratory reference value for baseline phosphate ≤0.70 mmol/L and >0.70 mmol/L, as high and low nutritional risk, respectively. Serum baseline prealbumin ≤0.10 g/L was considered as an indicator of severe nutritional risk, >0.10 and ≤0.15 g/L mild to moderate risk, and >0.15 g/L no risk.(14, 15) Baseline transferrin values of ≤1.0 g/L were considered as an indicator of severe nutritional risk, and >1 g/L no to moderate nutritional risk.(15) We categorized patients based on UUN using the median of the

cohort as a cutoff value. We calculated nitrogen balance on day 1 as follows: total protein intake in grams/6.25 – (UUN in mmol/35.7)+ 4 grams. A negative balance (≤0) is a marker of catabolism, and a positive balance (>0) indicates anabolism.(11) Baseline phosphate, prealbumin, transferrin were obtained at the time of enrollment. Baseline UUN was collected in the first 24 hours after enrollment.

Outcomes

For the high and low nutritional risk groups categorized by NUTRIC score, we compared the permissive underfeeding and the standard feeding groups for the primary endpoint of 90-day mortality. Secondary outcomes included ICU, 28-day, hospital and 180-day mortality, mechanical ventilation duration, ICU and hospital lengths of stay (LOS), hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, packed red blood cells (PRBC) transfusions, feeding intolerance and diarrhea in the first 14 ICU days and ICU- associated infections during the ICU stay (using published definitions (16)). Between the permissive underfeeding and standard feeding groups, we compared SOFA score, serum phosphate and potassium, prealbumin, transferrin, UUN, nitrogen balance, bilirubin, partial pressure of arterial carbon dioxide ($PaCO_2$), hemoglobin and weight, and examined changes in these variables over time. We conducted additional analyses to examine high and low nutritional risk categories using other definitions for 90-day mortality as a primary outcome and ICU-associated infections and incident renal replacement therapy (RRT) as secondary outcomes. As our analysis showed that prealbumin was a significant effect modifier of the association of the feeding intervention and mortality, we performed supplementary analyses of baseline characteristics, intervention and outcomes stratified by prealbumin level.

Statistical Analysis

Categorical variables were compared using the Chi-square test. Continuous variables were tested for normality; accordingly they were reported as means and standard deviation (SD) or medians and quartiles 1 and 3 (Q1-3) and were tested using the Student's t-test or Wilcoxon-Mann-Whitney test. Confounding effect is expected to have been controlled by the randomized design of the original study, which is expected to be true for the current analyses (stratified by variables based on baseline characteristics). Nevertheless, to further control for any residual confounding effect, we examined the association of the intervention and different outcomes after adjustment for a priori selected variables known to be clinically associated with the outcome (APACHE II, baseline creatinine and sepsis) using

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logistic and linear regression analyses, as appropriate. Variables were maintained in the model if p-value was <0.25. Results of the associations were reported as adjusted odds ratio (aOR) or correlation coefficient and 95% confidence intervals (95% CI). We added an interaction term to test for effect modification of the nutritional risk group on the association of the intervention and outcomes. Kaplan-Meier survival curves were compared using the log rank test. For serial measurements, we tested change over time and the difference between the two groups over time using repeated measures analysis of variance with no imputation for missing values. We performed retrospective power analyses to provide an indication of the smallest difference between the intervention and control groups in the two nutritional risk categories. In the high nutritional risk group, the available sample size (189 in each group) would yield 80% power to detect a 14.4% difference in 90-day mortality. In the low nutritional risk group, the available sample size (259 and 257 patients in the two study groups) would yield an 80% power to detect an 8.8% difference in 90-day mortality. Tests were two-sided and statistical significance was determined at p< 0.025 as per the Bonferroni correction for multiple testing. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient Characteristics: Of the 894 patients, 378 (42.3%) were categorized as high nutritional risk (NUTRIC Score 5-9) and 516 (57.7%) patients as low nutritional risk (NUTRIC Score 0-4). In each nutritional risk category, demographic, physiologic and nutritional characteristics of patients randomized to the permissive underfeeding and standard feeding groups were similar **(Table 1)**.

Feeding data and Co-interventions. In both NUTRIC nutritional risk categories, patients in the permissive underfeeding group received fewer calories than the standard feeding group, however both groups received similar protein throughout the study period (**Table 2, Figure 1**). Other co-interventions and nutrition-related data are shown in **Table 2 and Figure 1.**

Mortality. The association between permissive underfeeding versus standard feeding and mortality was non-significant in the two categories; aOR 0.84 (95% CI 0.56-1.27) for high nutritional risk and aOR 1.01 (95% CI 0.64-1.61) for low nutritional risk (interaction p=0.53) (**Table 3**). Similarly, there were no differences in ICU, hospital, 28-day or 180-day mortality between the two groups. Kaplan Meier survival

estimates demonstrated no difference in the probability of survival between the two groups in either nutritional risk categories (**Figure 2**).

Other Endpoints. In patients at high nutritional risk, incident RRT was less frequent in the permissive underfeeding group (22/153, 14.4%) compared with the standard feeding group [35/148, 23.7%; aOR 0.45 (95% CI 0.23-0.89), p=0.02)]. However, in patients at low nutritional risk, incident RRT was not statistically different in the permissive underfeeding group (7/253, 2.8%) compared to the standard feeding group [10/248, 4.0%; aOR 0.55 (0.18-1.66), p=0.29]. Test of interaction showed that the association of the intervention and incident RRT was not modified by the nutritional risk category (p-value for interaction=0.61). Serial SOFA scores, and prealbumin, nitrogen balance, phosphate, creatinine, bilirubin, $PaCO_2$, hemoglobin, body weight, potassium, transferrin, and UUN did not differ between the two groups in either nutritional risk category (**Figures 1 and Supplementary Appendix S1**). There were no differences in any other variables, including mechanical ventilation duration and ICU LOS, between the two groups in either nutritional risk category (**Table 3**).

Analyses Using Other Definitions for Nutritional risk

The associations of the intervention with 90-day mortality, ICU-associated infections and incident RRT were not modified by the nutritional risk category using other nutritional status indicators, including BMI, phosphate, transferrin 24-hour UUN and nitrogen balance. The only exception was prealbumin; the association of permissive underfeeding versus standard feeding with 90-day mortality differed by baseline prealbumin level; (prealbumin ≤ 0.10 g/L aOR 0.57, 95% CI 0.31-1.05, p=0.07; prealbumin >0.10 and ≤0.15 g/L aOR 0.79, 95% CI 0.42-1.48, p=0.46; prealbumin > 0.15 g/L aOR 1.55, 95% CI 0.79-3.01, p=0.20; p-value for interaction=0.009). The association between the intervention and incident RRT and ICU-associated infections did not differ across prealbumin groups. Detailed stratified analysis based on prealbumin categories of baseline characteristics, interventions and outcomes is provided in the Supplementary Tables S1, S2 and S3.

Discussion

In patients at high and low nutritional risk defined by the NUTRIC score, enteral feeding to deliver moderate non-protein calories was associated with similar mortality compared with planned delivery of full non-protein caloric requirements. Our study shows that most current definitions for nutritional risk, including the NUTRIC score,

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could not differentiate the risk association between moderate versus full caloric intake and outcomes. However, permissive underfeeding compared to standard feeding had different effects based on baseline prealbumin; patients with low prealbumin levels may have lower 90-day mortality if they received permissive underfeeding compared to standard feeding.

Our study indicates the limitations of available measures proposed for assessing nutritional risk. We found no difference in mortality or any other studied endpoint between high and low nutritional risk groups defined by NUTRIC or most other measures. The NUTRIC score, which is based on non-nutritional data, has been proposed for this purpose based on the finding of improved survival in patients with high NUTRIC scores in a post hoc analysis of an 1199-patient RCT.(5) However, our study does not validate this finding, as we found that the NUTRIC score cannot be used to differentiate between who may or may not benefit from different caloric dosing. Given that nutritional adequacy was defined retrospectively in the observational cohort,(5) the influence of residual confounding effects cannot be excluded, which is probably responsible for the discordant results of many observational nutritional studies in critical care. Among all examined indicators in our study, baseline prealbumin differentiated the risk association of permissive underfeeding and mortality; patients with low prealbumin had lower mortality with permissive underfeeding compared to standard feeding. The use of admission prealbumin level to predict response to nutrition has also been demonstrated in a study of hospitalized patients with anorexia nervosa; patients with low prealbumin had a threefold risk of refeeding hypophosphatemia and a twofold risk of hypoglycemia compared with patients with normal prealbumin, independent of BMI (17). However, we did not find differences in the incidence of hypophosphatemia or hypoglycemia in our study based on prealbumin levels.

The risk of inducing refeeding syndrome, defined as hypophosphatemia after reinstituting nutritional support, in malnourished ICU patients has been a concern.(18-20) We found no difference in serial phosphate, potassium and magnesium levels between permissive underfeeding and standard feeding groups in both the high and low nutritional risk categories defined by NUTRIC score. A recent RCT of restricted versus continued standard caloric intake in patients with refeeding syndrome found that the restricted caloric group had slightly higher phosphate level on days 1 and 2 (difference of 0.1 mmol/L), although phosphate replacement dose and the number of patients receiving phosphate replacement did not differ between

study groups.(7) Interestingly, the trial showed that this high-risk group with refeeding syndrome had higher hospital survival with restricted caloric feeding compared to standard feeding (91% versus 82%, absolute risk difference 9.2%, 95% CI: 0.7-17.7, p=0.017), although mortality was a secondary endpoint for the trial. (7) These findings are in line with our observation regarding prealbumin, that certain patients with high nutritional risk may have better outcomes with a restricted nutritional strategy.

In both the high and low nutritional risk groups as defined by the NUTRIC scores, we found no differences between permissive underfeeding and standard feeding in indices of protein status including prealbumin, transferrin levels, UUN and nitrogen balance, keeping in mind the limitations of these parameters in assessing protein metabolism.(21)

We also found no differences in ICU-acquired infections with permissive underfeeding versus standard feeding in high or low nutritional risk categories. In a recent trial of restricted versus continued standard caloric intake in patients with refeeding syndrome, the restricted caloric strategy was associated with a lower incidence of infections than the standard feeding strategy.(7) However, this trial did not include patients with no refeeding syndrome, therefore one cannot conclude whether refeeding syndrome defined by post-feeding hypophosphatemia is an effect modifier of the caloric dose on outcomes.

In patients with high nutritional risk (NUTRIC scores 5-9), those allocated to permissive underfeeding had lower utilization of incident RRT. Indeed, caloric restriction has been shown to be renal-protective in animal models of acute kidney injury,(22-24) via several mechanisms including improved insulin sensitivity.(24) Our findings suggest a need for further research on the optimal caloric dose in critically ill patients with or at risk for acute kidney injury.

It is important to note that the PermiT trial restricted calories and not protein. In contrast, the EDEN study limited both calories and protein.(1) The effects of both protein and caloric restriction and whether the dose of protein affects outcomes in patients with high nutritional risk remains to be studied.

The strengths of this study include the multicenter conduct and the pragmatic inclusion of medical-surgical-trauma critically ill adults, all of whom received early

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initiation of feeding. Additionally, the baseline characteristics of the groups of permissive underfeeding and standard feeding were balanced in both high and low malnutrition categories defined by NUTRIC score. A limitation of this study is the post-hoc analysis. Given the number of statistical tests, the significant associations observed with prealbumin could be related to multiple testing. Our study did not address whether permissive underfeeding versus standard feeding has a differential effect on long-term outcome based on underlying nutritional status.

Regarding nutrition and long-term outcomes, an observational study of 302 adults receiving prolonged mechanical ventilation (>8 days in the ICU) found that receiving adequate energy in the first eight days of ICU stay was associated with improved health related quality of life at three-months, although this association became non-significant by six-months.(25) However, average BMI in the study population was 30.0±8.7 kg/m^2 and only 2% had BMI <18.5 kg/m^2, therefore the results may not be generalizable to patients with low BMI. In a sub-study of the EDEN trial, 174 acute lung injury survivors (mean BMI 32 kg/m^2) underwent long-term follow up with physical and cognitive evaluation.(26) At 6 and 12 months, initial trophic versus full enteral feeding had no effect on either physical performance outcomes (upper arm anthropometrics, muscle strength, pulmonary function, 6-min-walk distance) or cognitive function.(26) However, the EDEN study enrolled relatively young and overweight patients, and excluded underweight patients; therefore, the results of this study may not be generalizable to other ICU patients. Additionally, there was no stratification by baseline nutritional status. Therefore, whether moderate versus full caloric intake has different effects in patients with high and low nutritional risk on long-term functional and cognitive function remains largely unknown and deserves further study.

In conclusion, in patients with high and low nutritional risk alike, enteral feeding to deliver moderate calories with full protein intake was associated with similar mortality compared with standard caloric feeding with full protein requirements. Available nutritional assessment measures do not appear to differentiate the risk association of moderate versus full caloric doses on mortality.

Figure 1. Serial measurements of the intervention, co-interventions and selected outcomes in patients randomized to permissive underfeeding and standard feeding groups with startification to high (NUTRIC score 5-9) and the low nutritional risk (NUTRIC score 0-4). Means and 95% confidence intervals are displayed. * denotes statistical significance for the difference between the two groups on each day. P values for the change over time for both groups combined and for the difference between the two groups over time using repeated measures analysis of variance are given for each variable in the high and the low nutritional risk groups. Total scores on the Sequential Organ Failure Assessment (SOFA) range from 0 to 24, with higher scores indicating a greater degree of organ failure. Nitrogen balance was calculated as [total protein intake in grams ÷ 6.25] – [(urinary nitrogen excretion (UUN) in millimoles ÷ 35.7) + 4 g].

Figure 2: Kaplan-Meier survival curves for patients in the permissive underfeeding and standard feeding groups stratified by NUTRIC score (high nutritional risk: NUTRIC score 5-9 and low nutritional risk: NUTRIC score 0-4) and by prealbumin.

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Table 1: Baseline characteristics of patients with high (NUTRIC score 5-9) and low nutritional risk (NUTRIC score 0-4) randomized to permissive underfeeding and standard feeding.

Variable	High nutritional risk group (NUTRIC 5-9) N= 378			Low nutritional risk group (NUTRIC 0-4) N=516		
	Permissive underfeeding N=189	Standard feeding N=189	P-value	Permissive underfeeding N=259	Standard feeding N=257	P-value
Age– (yr) (mean±SD)	60±17	63±14	0.06	43±18	42±18	0.49
Female sex– no. (%)	87 (46.0)	81 (42.9)	0.53	69 (26.6)	83 (32.3)	0.16
Admission category– no. (%)						
Medical	175 (92.6)	170 (90.0)		161 (62.2)	165 (64.2)	
Surgical	2 (1.1)	5 (2.7)	0.47	17 (6.6)	7 (2.7)	0.12
Non-operative trauma	12 (6.4)	14 (7.4)		81 (31.3)	85 (33.1)	
Diabetes– no. (%)	104 (55.0)	103 (54.5)	0.92	55 (21.2)	50 (19.5)	0.62
Sepsis– no. (%)	106 (56.1)	90 (47.6)	0.10	53 (20.5)	43 (16.7)	0.28
Traumatic brain injury– no. (%)	7 (3.7)	8 (4.2)	0.79	48 (18.5)	55 (21.4)	0.42
APACHE II score– (median (Q1, Q3))*	26 (22, 31)	27 (22, 31)	0.46	17 (13, 20)	17 (12, 20)	0.71
SOFA score on day 1– (mean±SD)	11.8±3.0	11.6±3.1	0.49	8.5±3.1	8.5±3.2	0.90
Mechanical ventilation– no. (%)	186 (98.4)	181 (95.8)	0.13	250 (96.5)	248 (96.5)	0.99
Vasopressor– no. (%)	116 (61.4)	119 (63.0)	0.75	139 (53.7)	124 (48.3)	0.22
Renal replacement therapy– no. (%)	35 (18.5)	41 (21.7)	0.44	6 (2.3)	8 (3.1)	0.58
Inclusion blood glucose– (mg/dL) (median (Q1,Q3))*	199 (146, 262)	187 (141, 246)	0.35	155 (124, 200)	151 (121, 211)	0.94
Inclusion blood glucose– (mmol/L) (median (Q1,Q3))*	11.1 (8.1, 14.6)	10.4 (7.9, 13.7)	0.35	8.6 (6.9, 11.1)	8.4 (6.7, 11.7)	0.94
Creatinine– (mg/dL) (median (Q1, Q3))*	1.44 (0.85, 2.67)	1.53 (0.94, 3.04)	0.20	0.84 (0.69, 1.06)	0.78 (0.67, 1.09)	0.20
Creatinine– (µmol/L) (median (Q1, Q3))*	127 (75, 236)	135 (83, 269)	0.20	74 (61, 94)	69 (59, 96)	0.20
Bilirubin– (mg/dL) (median (Q1, Q3))*	0.87 (0.51, 1.80)	0.91 (0.52, 1.71)	1.0	0.70 (0.47, 1.25)	0.76 (0.48, 1.24)	0.61
Bilirubin– (µmol/L) (median (Q1, Q3))*	14.9 (8.8, 30.9)	15.6 (8.9, 29.3)	1.0	11.9 (8.0, 21.4)	13.0 (8.2, 21.2)	0.61
Platelets– (10^9/L) (median (Q1, Q3))*	146 (83, 240)	183 (98, 278)	0.01	200 (141, 262)	199 (147, 252)	0.80
INR– (median (Q1, Q3))*	1.3 (1.1, 1.5)	1.3 (1.1, 1.6)	0.31	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.65
C-reactive Protein– (mg/L) (mean±SD)†	127±86	133±91	0.56	133±76	119±74	0.05
Hemoglobin– (g/L) (mean±SD)	99±22	101±21	0.49	109±23	110±23	0.53
BMI– (kg/m^2) (median (Q1, Q3))*	27.7 (23.5, 35.0)	28.7 (24.6, 34.9)	0.35	27.1 (23.1, 32.0)	27.3 (23.5, 32.0)	0.58
NUTRIC score– (mean±SD)	5.88±0.88	5.94±0.97	0.54	2.88±1.09	2.86±1.06	0.86
Phosphate– (mmol/L) (mean±SD)†	1.14±0.57	1.12±0.51	0.79	0.86±0.33	0.90±0.35	0.14
Albumin– (g/L) (mean±SD)	27.6±8.6	26.7±5.9	0.24	28.4±5.8	29.3±5.6	0.08
Prealbumin– (g/L) (median (Q1, Q3))†	0.11 (0.08, 0.16)	0.10 (0.07, 0.14)	0.04*	0.13 (0.10, 0.16)	0.13 (0.11, 0.17)	0.29*
Transferrin– (g/L) (mean±SD)†	1.29±0.53	1.22±0.49	0.20	1.40±0.44	1.49±0.48	0.05
24 hours urinary urea nitrogen– (mmol) (median (Q1,Q3))†*	229 (104, 377)	199 (108, 314)	0.15	268 (197, 383)	286 (205, 422)	0.13
Nitrogen balance– (g) (mean±SD)†	-4.40±6.42	-3.76±6.02	0.44	-5.85±5.37	-6.48±7.03	0.33
Time from eligibility to randomization– (hours) (median (Q1, Q3))*	4.0 (0.0, 17.0)	2.3 (0.0, 13.1)	0.16	2.0 (0.0, 12.0)	1.0 (0.0, 11.7)	0.68

APACHE II: Acute Physiology and Chronic Health Evaluation II; **SOFA**: Sequential Organ Failure Assessment; **INR:** International normalized ratio; **BMI**: Body mass index; **SD**: standard deviation; **Q**: quartile; **NUTRIC:** NUTrition Risk in the Critically ill

NUTRIC score ranges from1-9 based on age, APACHE, SOFA, number of comorbidities and days from hospital to ICU admission.

*Testing using Wilcoxon-Mann-Whitney test

†Data on laboratory values were not available for some patients; the numbers of patients with available data were as follows: C-reactive protein, 717 patients; prealbumin, 675 patients; transferrin, 720 patients; 24-hour urinary nitrogen excretion, 597 patients; phosphate, 854 patients; nitrogen balance, 596 patients.

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Table 2: Study interventions and co-interventions in patients with high (NUTRIC score 5-9) and low nutritional risk (NUTRIC score 0-4) randomized to permissive underfeeding and standard feeding.

Variable	High nutritional risk group N= 378			Low nutritional risk group N= 516		
	Permissive underfeeding N=189	Standard feeding N=189	P-value	Permissive underfeeding N=259	Standard feeding N=257	P-value
Interventions						
Calculated caloric requirement–(kcal/day) (mean±SD)	1747±355	1744±336	0.93	1877±384	1916±377	0.26
Study caloric target–(kcal/day) (mean±SD)	987±243	1736±340	<0.0001	1073±270	1893±386	<0.0001
Achieved daily caloric intake–(kcal) (mean±SD)	799±277	1216±420	<0.0001	862±308	1360±491	<0.0001
% of requirement achieved–(mean±SD)	45.8±12.3	70.7±22.7	<0.0001	46.4±14.8	71.1±21.3	<0.0001
Caloric source–(kcal) (mean±SD)						
Enteral	719±271	1137±427	<0.0001	756±309	1243±495	<0.0001
Propofol*†	45.2±72.7	45.1±73.7	0.97	76.6±96.0	78.9±95.6	0.82
Dextrose*†	34.1±50.4	35.2±58.2	0.83	31.0±64.6	34.6±61.4	0.08
PN*†	4.8±46.4	3.6±41.0	0.71	1.0±14.7	6.5±69.4	0.39
Calculated protein requirement–(g/day) (mean±SD)	82.7±22.0	82.2±21.2	0.83	87.1±20.6	91.5±23.1	0.02
Achieved protein intake–(g/day) (mean±SD)	55.6±22.1	54.4±22.5	0.62	58.5±25.1	62.8±26.1	0.06
% of requirement achieved–(mean±SD)	68.4±23.3	68.0±26.8	0.89	68.1±25.2	69.1±24.3	0.65
Duration of intervention–(days) (mean±SD)	9.2±4.4	9.6±4.3	0.36	9.0±4.6	9.2±4.4	0.51
Co-interventions						
Received insulin–no. (%)	122 (64.6)	137 (72.5)	0.10	83 (32.1)	98 (38.1)	0.15
Daily insulin dose–(units) (median (Q1,Q3))*	8.2 (0.0, 36.5)	17.6 (0.0, 39.9)	0.07	0.0 (0.0, 6.8)	0.0 (0.0, 10.8)	0.12
Formulae–no. (%)						
Disease non-specific	72 (38.1)	63 (33.3)	0.33	198 (76.5)	180 (70.0)	0.10
Disease specific	117 (61.9)	126 (66.7)		61 (23.6)	77 (30.0)	

PN: Parenteral nutrition; **Disease-Non-Specific formula**: Osmolite, Jevity, Promote, Ensure plus, Resourse, Ensure, Resource plus, Jevity(1.2);
Disease Specific formula: Glucerna, Nutric hepatic, Nepro, Pulmocare, Novasource Renal, Peptamen(1.0), Peptamen(1.2), Suplena, Oxepa
*Testing using Wilcoxon-Mann-Whitney test.
†Calories from propofol, dextrose and PN are reported as means±SD although they are not normally distributed to be consistent with other variables related to calories which were normally distributed.

Table 3: Outcome data of patients with high (NUTRIC score 5-9) and low nutritional risk (NUTRIC score 0-4) randomized to permissive underfeeding and standard feeding. The association with different outcomes was adjusted to APACHE II score, creatinine level and sepsis and is reported as adjusted odds ratio (aOR) with 95% confidence intervals (CI).

Outcomes	High nutritional risk group N= 378				Low nutritional risk group N= 516				
	Permissive underfeeding N=189	Standard feeding N=189	Adjusted odds ratio or correlation coefficient (95% CI)	P-value	Permissive underfeeding N=259	Standard feeding N=257	Adjusted odds ratio or correlation coefficient (95% CI)	P-value	P-value for inter-action
28-day mortality–no. (%)	56/189 (29.6)	59/189 (31.2)	0.93 (0.60, 1.44)	0.74	37/258 (14.3)	38/255 (14.9)	0.93 (0.56, 1.53)	0.76	0.93
90-day mortality–no. (%)	75/189 (39.7)	83/189 (43.9)	0.84 (0.56, 1.27)	0.40	46/256 (18.0)	44/251 (17.5)	1.01 (0.64, 1.61)	0.96	0.53
180-day mortality–no. (%)	81/188 (43.1)	90/189 (47.6)	0.86 (0.57, 1.29)	0.45	50/250 (20.0)	50/247 (20.2)	0.96 (0.61, 1.50)	0.85	0.60
ICU mortality–no. (%)	43/189 (22.8)	51/189 (27.0)	0.80 (0.50, 1.27)	0.34	29/259 (11.2)	34/257 (13.2)	0.82 (0.48, 1.39)	0.46	0.91
Hospital mortality–no. (%)	67/188 (35.6)	80/189 (42.3)	0.73 (0.48, 1.11)	0.14	41/259 (15.8)	43/256 (16.8)	0.90 (0.56, 1.45)	0.67	0.50
ICU LOS–(days) (median (Q1,Q3))	13.0 (8.0, 21.0)	14 (9.0, 22.0)	-1.4 (-4.0, 1.3)	0.30	13.0 (7.0, 20.0)	13.0 (8.0, 19.0)	-0.04 (-1.9, 1.8)	0.96	0.39
Hospital LOS–(days) (median (Q1,Q3))	29.0 (16.0, 52.5)	35.0 (17.0, 62.0)	-8.5 (-21.5, 4.4)	0.20	27.0 (14.0, 55.0)	27.0 (13.0, 65.0)	-5.2 (-18.2, 7.9)	0.44	0.72
Ventilation duration–(days) (median (Q1,Q3))	9.0 (6.0, 16.0)	10.0 (5.0, 17.0)	-1.9 (-4.7, 0.9)	0.18	9.0 (5.0, 14.0)	9.0 (5.0, 15.0)	-2.6 (-5.9, 0.7)	0.13	0.72
PRBC transfusions–no. (%)	81/189 (42.9)	82/189 (43.4)	1.02 (0.67, 1.53)	0.94	60/259 (23.2)	60/257 (23.4)	0.97 (0.64, 1.47)	0.89	0.90
Cumulative PRBC transfusion over 14 days–(units) (mean±SD)	0.17±0.37	0.15±0.25	0.01 (-0.05, 0.08)	0.72	0.10±0.20	0.10±0.30	-0.02 (-0.06, 0.02)	0.41	0.46
Hypoglycemia–no. (%)	6/189 (3.2)	5/189 (2.7)	1.22 (0.37, 4.09)	0.75	0/259 (0.0)	2/257 (0.80)	NA	NA	NA
Hypokalemia–no. (%)	44/189 (23.3)	50/189 (26.5)	0.80 (0.49, 1.28)	0.34	57/259 (22.0)	41/257(16.0)	1.48 (0.95, 2.32)	0.08	0.06
Hypomagnesemia–no. (%)	44/189 (23.3)	59/189 (31.2)	0.67 (0.42, 1.06)	0.08	83/259 (32.1)	72/257 (28.0)	1.21 (0.83, 1.77)	0.32	0.05
Hypophosphatemia–no. (%)	108/189 (57.1)	99/189 (52.4)	1.16 (0.76, 1.75)	0.49	159/259 (61.4)	162/257 (63.0)	0.96 (0.67, 1.37)	0.81	0.46
Incident renal replacement therapy–no. (%)	22/153 (14.4)	35/148 (23.7)	0.45 (0.23, 0.89)	0.02	7/253 (2.8)	10/248 (4.0)	0.55 (0.18, 1.66)	0.29	0.61
Healthcare-associated infections–no. (%)	66/189 (34.9)	73/189 (38.6)	0.85 (0.56, 1.30)	0.46	95/259 (36.7)	96/257 (37.4)	0.99 (0.69, 1.41)	0.94	0.60
Urinary tract infection–no. (%)	28/189 (14.8)	25/189 (13.2)	1.12 (0.63, 2.02)	0.70	17/259 (6.6)	23/257 (9.0)	0.72 (0.37, 1.37)	0.31	0.36
Catheter-related bloodstream infection–no. (%)	2/189 (1.1)	8/189 (4.2)	0.24 (0.05, 1.16)	0.08	9/259 (3.5)	11/257 (4.3)	0.81 (0.33, 1.98)	0.64	0.19
Ventilator associated pneumonia–no. (%)	25/189 (13.2)	33/189 (17.5)	0.72 (0.41, 1.27)	0.25	56/259 (21.6)	57/257 (22.2)	0.99 (0.65, 1.51)	0.95	0.41
ICU-associated severe sepsis or septic shock–no. (%)	1/189 (0.5)	1/189 (0.5)	1.7 (0.09, 33.17)	0.73	2/259 (0.8)	1/257 (0.4)	1.99 (0.18, 22.11)	0.57	0.73
Feeding intolerance–no. (%)	36/189 (19.1)	37/189 (19.6)	0.97 (0.58, 1.61)	0.90	31/259 (12.0)	42/257 (16.3)	0.71 (0.43, 1.17)	0.18	0.34
Diarrhea–no. (%)	55/189 (29.1)	66/189 (34.9)	0.77 (0.50, 1.18)	0.23	42/259 (16.2)	51/257 (19.8)	0.75 (0.48, 1.18)	0.22	0.86

ICU: intensive care unit**; LOS:** length of stay; **PRBC**: Packed red blood cell; **NA**: not applicable
Hypoglycemia: defined as blood glucose levels below 2.2 mmol/L; **Hypokalemia:** defined as drop in potassium to less than 2.8 mmol/L; **Hypomagnesemia**: defined as drop in magnesium to less than 0.60 mmol/L**;** **Hypophosphatemia**: defined as drop in phosphate to less than 0.70 mmol/L; **Feeding intolerance**: defined as vomiting, abdominal distention, or a gastric residual volume of more than 200 ml; **Diarrhea**: defined as three or more loose or liquid stools per day for 2 consecutive days.

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Table 4: Additional analyses of outcome of patients randomized to permissive underfeeding and standard feeding as categorized by nutritional risk definitions other than NUTRIC.

Variables, no. (%)	Permissive underfeeding	Standard feeding	Adjusted odds ratio (95% CI)	P-value	P-value for interaction
90-day mortality*					
BMI < 18.5 kg/m^2	7/22 (31.8)	4/19 (21.1)	3.95 (0.51, 30.47)	0.19	
BMI 18.5 - 24.9 kg/m^2	36/128 (28.1)	39/116 (33.6)	0.76 (0.43, 1.34)	0.34	
BMI 25.0 - 29.9 kg/m^2	36/127 (28.4)	31/133 (23.3)	1.27 (0.72, 2.26)	0.41	0.36
BMI 30 - 39.9 kg/m^2	33/128 (25.8)	38/125 (30.4)	0.88 (0.49, 1.56)	0.66	
BMI ≥ 40 kg/m^2	9/40 (22.5)	14/46 (30.4)	0.38 (0.12, 1.17)	0.09	
Phosphate ≤ 0.70 mmol/L	29/125 (23.2)	23/110 (20.9)	1.36 (0.71, 2.62)	0.36	0.13
Phosphate > 0.70 mmol/L	84/298 (28.2)	97/313 (31.0)	0.77 (0.54, 1.11)	0.16	
Prealbumin ≤ 0.10 g/L	28/98 (28.6)	45/102 (44.1)	0.57 (0.31, 1.05)	0.07	
Prealbumin > 0.10 and ≤ 0.15 g/L	23/124 (18.6)	30/128 (23.4)	0.79 (0.42, 1.48)	0.46	0.009
Prealbumin > 0.15 g/L	30/111 (27.0)	19/108 (17.6)	1.55 (0.80, 3.01)	0.20	
Transferrin ≤ 1.0 g/L	38/90 (42.2)	36/89 (40.5)	0.99 (0.52, 1.87)	0.97	0.54
Transferrin > 1.0 g/L	52/268 (19.4)	61/269 (22.7)	0.83 (0.54, 1.26)	0.35	
24- hour urinary urea nitrogen ≤ 262.5 mmol	49/160 (30.6)	44/146 (30.1)	0.92 (0.55, 1.53)	0.74	
24- hour urinary urea nitrogen > 262.5 mmol	27/143 (18.9)	27/143 (18.9)	0.89 (0.48, 1.64)	0.71	0.99
Negative nitrogen balance	58/258 (22.5)	53/235 (22.6)	0.75 (0.46, 1.23)	0.25	0.78
Positive nitrogen balance	18/44 (40.9)	18/54 (33.3)	0.88 (0.33, 2.34)	0.79	
New renal replacement therapy					
BMI < 18.5 kg/m^2	3/22 (13.6)	1/17 (5.9)	NA	NA	
BMI 18.5 - 24.9 kg/m^2	4/119 (3.4)	9/108 (8.3)	0.38 (0.10, 1.43)	0.15	0.74
BMI 25.0 - 29.9 kg/m^2	2/116 (1.7)	13/125 (10.4)	0.05 (0.01, 0.43)	0.006	
BMI 30 - 39.9 kg/m^2	12/117 (10.3)	14/106 (13.2)	0.82 (0.29, 2.29)	0.70	
BMI ≥ 40 kg/m^2	8/32 (25.0)	7/39 (18.0)	0.48 (0.10, 2.27)	0.35	
Phosphate ≤ 0.70 mmol/L	2/117 (1.7)	5/105 (4.8)	0.40 (0.06, 2.72)	0.35	0.95
Phosphate > 0.70 mmol/L	27/270 (10.0)	37/278 (13.3)	0.51 (0.27, 0.95)	0.03	
Prealbumin ≤ 0.10 g/L	9/86 (10.5)	18/87 (20.7)	0.48 (1.18, 1.28)	0.14	0.08
Prealbumin > 0.10 and ≤ 0.15 g/L	5/116 (4.3)	13/117 (11.1)	0.24 (0.06, 0.91)	0.04	
Prealbumin > 0.15 g/L	9/101 (8.9)	5/103 (4.8)	2.24 (0.47, 10.62)	0.31	
Transferrin ≤ 1.0 g/L	15/80 (18.8)	12/72 (16.7)	1.34 (0.45, 4.01)	0.60	0.03
Transferrin > 1.0 g/L	11/249 (4.4)	25/253 (9.9)	0.32 (0.14, 0.76)	0.01	
24- hour urinary urea nitrogen ≤ 262.5 mmol	13/145 (9.0)	18/132 (13.6)	0.56 (0.23, 1.38)	0.21	0.77
24- hour urinary urea nitrogen > 262.5 mmol	4/141 (2.8)	7/142 (4.9)	0.59 (0.16, 2.17)	0.43	
Negative nitrogen balance	12/247 (4.9)	17/229 (7.4)	0.34 (0.13, 0.92)	0.03	0.74
Positive nitrogen balance	5/38 (13.2)	8/45 (17.8)	0.42 (0.05, 3.29)	0.41	

Variables, no. (%)	Permissive underfeeding	Standard feeding	Adjusted odds ratio (95% CI)	P-value	P-value for interaction
ICU-associated infections					
BMI < 18.5 kg/m^2	8/22 (36.4)	7/19 (36.8)	0.98 (0.27, 3.50)	0.97	0.35
BMI 18.5 - 24.9 kg/m^2	51/129 (39.5)	39/120 (32.5)	1.36 (0.81, 2.28)	0.25	
BMI 25.0 - 29.9 kg/m^2	45/127 (35.4)	57/133 (42.9)	0.73 (0.44, 1.22)	0.23	
BMI 30 - 39.9 kg/m^2	40/130 (30.8)	47/126 (37.3)	0.75 (0.45, 1.26)	0.27	
BMI ≥ 40 kg/m^2	17/40 (42.5)	19/47 (40.4)	0.92 (0.38, 2.26)	0.87	
Phosphate ≤ 0.70 mmol/L	57/126 (45.2)	41/111 (36.9)	1.41 (0.84, 2.38)	0.20	0.10
Phosphate > 0.70 mmol/L	102/300 (34.0)	120/317 (37.9)	0.84 (0.61, 1.17)	0.31	
Prealbumin ≤ 0.10 g/L	33/98 (33.7)	44/102 (43.1)	0.67 (0.38, 1.19)	0.17	0.42
Prealbumin > 0.10 and ≤ 0.15 g/L	62/125 (49.6)	52/129 (40.3)	1.46 (0.89, 2.40)	0.14	
Prealbumin > 0.15 g/L	42/111 (37.8)	43/110 (39.1)	1.00 (0.57, 1.74)	0.99	
Transferrin ≤ 1.0 g/L	34/90 (37.8)	37/89 (41.6)	0.85 (0.47, 1.55)	0.60	0.48
Transferrin > 1.0 g/L	107/269 (39.8)	107/272 (39.3)	1.02 (0.72, 1.44)	0.91	
24- hour urinary urea nitrogen ≤ 262.5 mmol	66/160 (41.3)	59/148 (39.9)	1.11 (0.70, 1.75)	0.67	0.58
24- hour urinary urea nitrogen > 262.5 mmol	61/145 (42.1)	53/144 (36.8)	1.25 (0.78, 2.00)	0.36	
Negative nitrogen balance	112/260 (43.1)	88/238 (37.0)	1.14 (0.77, 1.68)	0.52	0.23
Positive nitrogen balance	14/44 (31.8)	24/54 (44.4)	0.62 (0.26, 1.50)	0.29	

BMI: Body mass index**; CI:** confidence interval; **NA**: not applicable; *90-day mortality was not available in 9 patients

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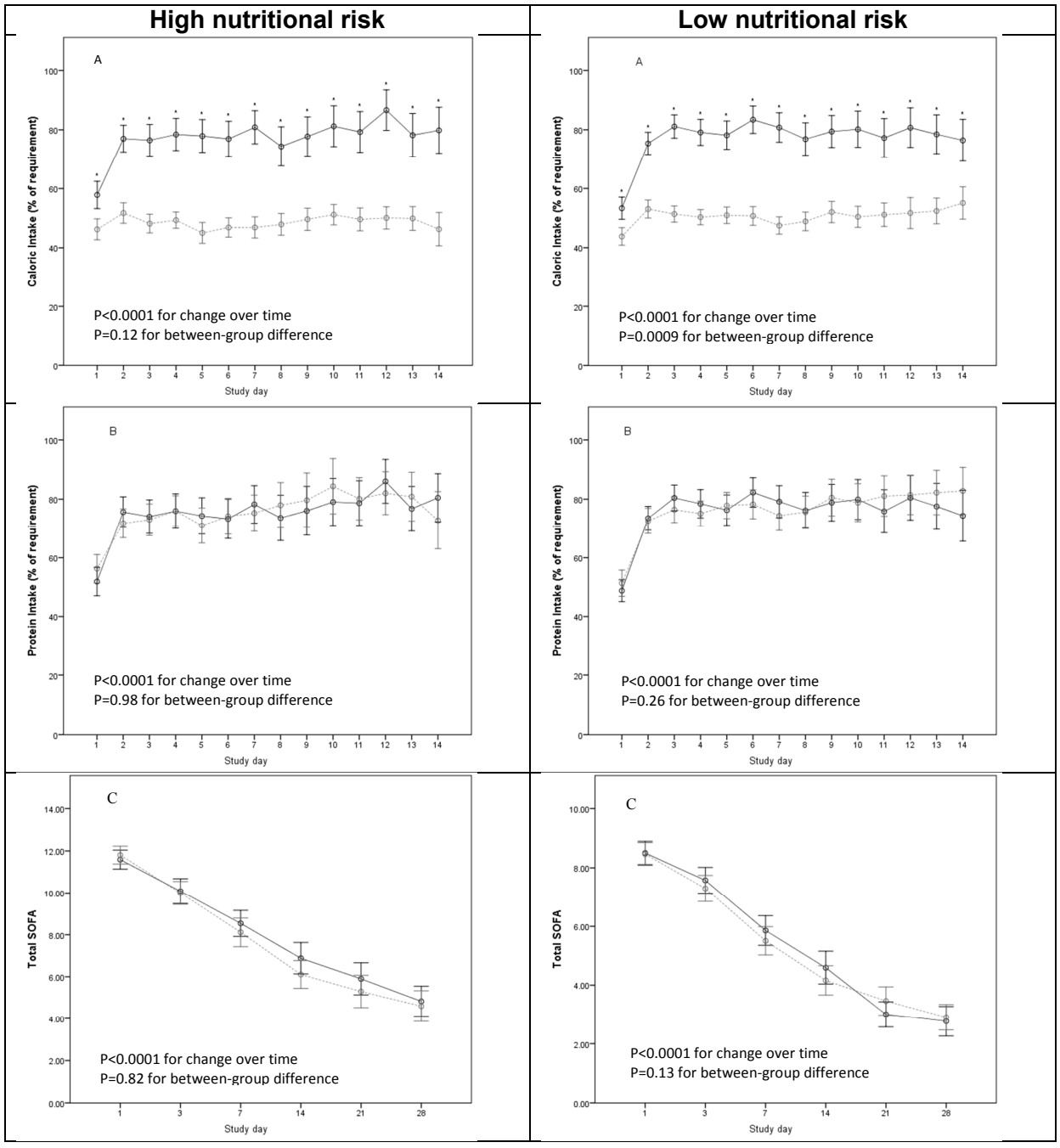
Figure 1



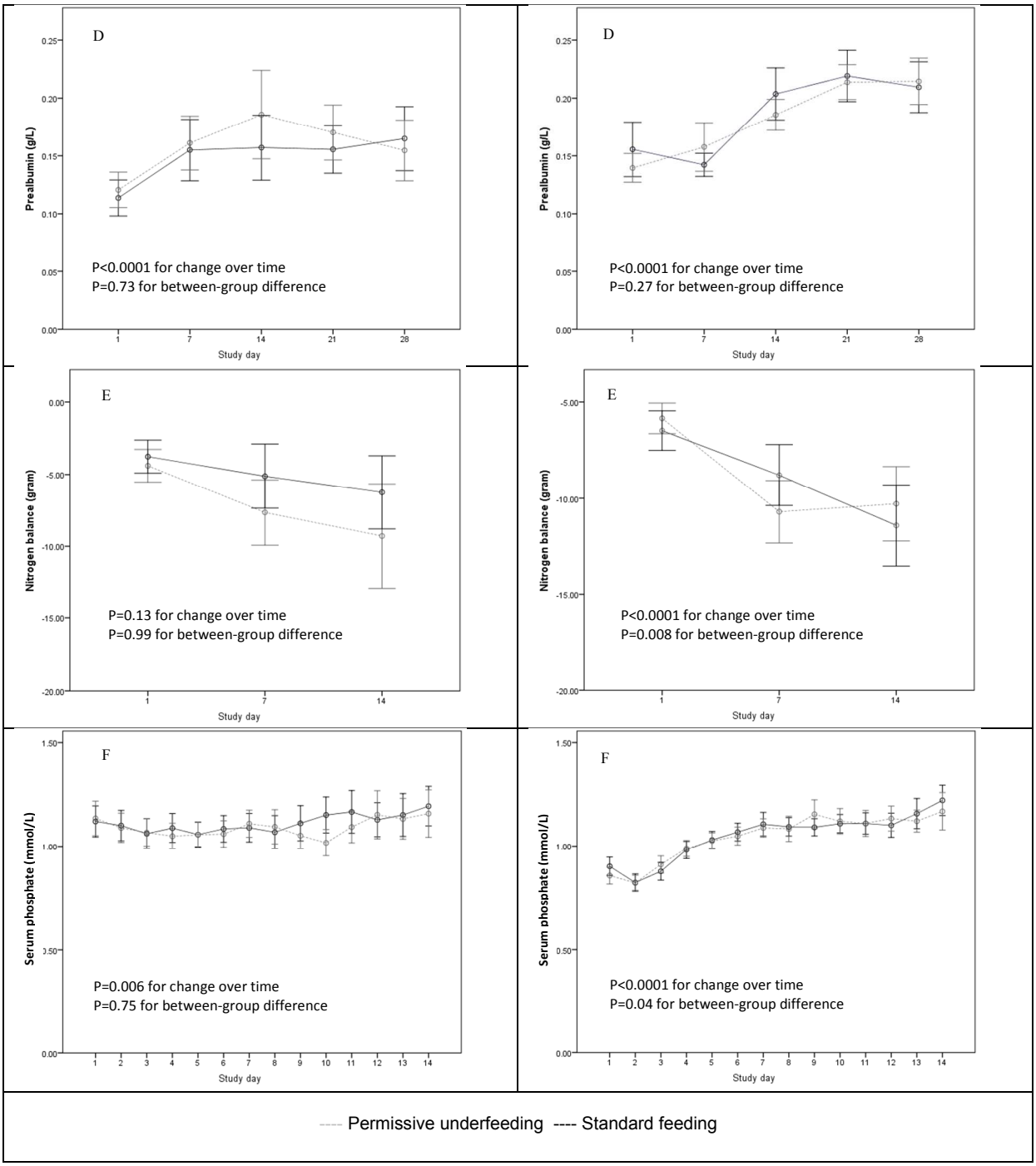


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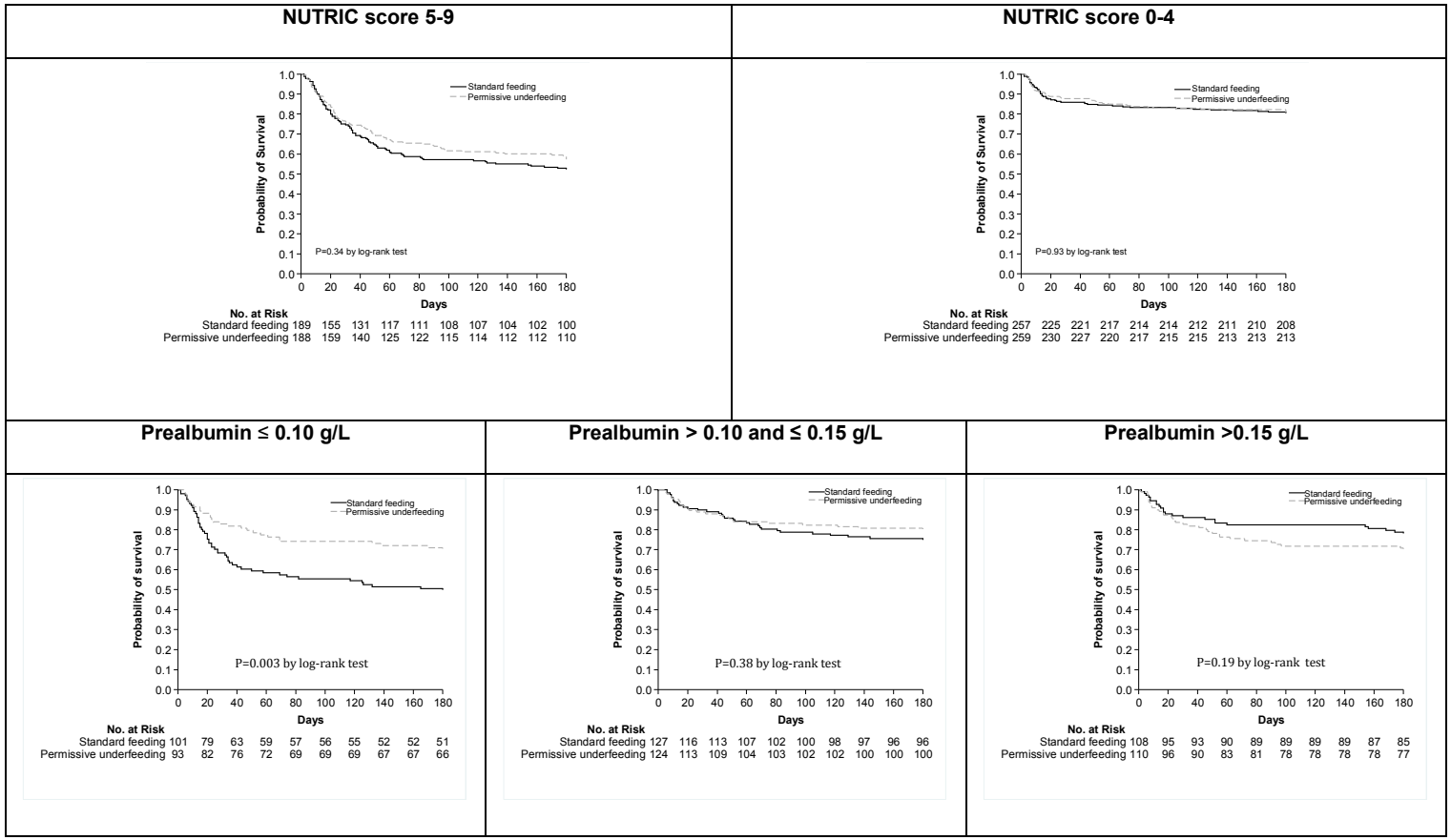
Figure 2



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Supplementary Appendix to

Permissive Underfeeding or Standard Enteral Feeding in High and Low Nutritional Risk Critically Ill Adults

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Supplement to the Results

Table S1. Baseline characteristics of patients stratified by prealbumin levels and randomized to permissive underfeeding or standard feeding.

Variable	Prealbumin ≤0.10 g/L N= 200			Prealbumin >0.10 and ≤0.15 g/L N=254			Prealbumin >0.15 g/L N=221		
	Permissive underfeeding N=98	Standard feeding N=102	P-value	Permissive underfeeding N=125	Standard feeding N=129	P-value	Permissive underfeeding N=111	Standard feeding N=110	P-value
Age– (yr) (mean±SD)	53.3±18.3	56.4±18.1	0.22	45.2±19.4	46.8±20.6	0.53	43.6±19.4	44.8±18.5	0.66
Female sex– no. (%)	39 (39.8)	40 (39.2)	0.93	35 (28.0)	38 (29.5)	0.80	28 (25.2)	37 (33.6)	0.17
Admission category– no. (%)									
Medical	81 (82.7)	87 (85.3)		79 (63.2)	83 (64.3)		75 (67.6)	71 (64.6)	
Surgical	5 (5.1)	2 (2.0)	0.48	5 (4.0)	5 (3.9)	0.98	5 (4.5)	3 (2.7)	0.61
Non-operative trauma	12 (12.2)	13 (12.8)		41 (32.8)	41 (31.8)		31 (27.9)	36 (32.7)	
Diabetes– no. (%)	43 (43.9)	46 (45.1)	0.86	44 (35.2)	47 (36.4)	0.84	36 (32.4)	29 (26.4)	0.32
Sepsis– no. (%)	54 (55.1)	42 (41.2)	0.05	27 (21.6)	30 (23.3)	0.75	31 (27.9)	17 (15.5)	0.02
Traumatic brain injury– no. (%)	3 (3.1)	3 (2.9)	1.0	21 (16.8)	32 (24.8)	0.12	25 (22.5)	23 (20.9)	0.77
APACHE II score– (mean±SD)	22.9±8.8	23.6±7.7	0.55	20.0±7.1	20.8±9.2	0.46	20.7±8.3	18.6±7.4	0.05
SOFA score on day 1– (mean±SD)	11.2±3.4	11.7±3.5	0.31	10.2±2.9	9.7±3.0	0.25	10.1±3.2	9.5±3.1	0.16
Mechanical ventilation– no. (%)	96 (98.0)	100 (98.0)	1.0	121 (96.8)	122 (94.6)	0.38	109 (98.2)	104 (94.6)	0.17
Vasopressor– no. (%)	63 (64.3)	61 (59.8)	0.51	72 (57.6)	73 (56.6)	0.87	63 (56.8)	55 (50.0)	0.31
Renal replacement therapy– no. (%)	12 (12.2)	15 (14.7)	0.61	9 (7.2)	12 (9.3)	0.54	9 (8.1)	7 (6.4)	0.62
Inclusion blood glucose– (mg/dL) (median (Q1, Q3))*	172 (124, 238)	186 (133, 265)	0.59	173 (137, 238)	162 (128, 216)	0.09	171 (137, 207)	159 (124, 225)	0.28
Inclusion blood glucose– (mmol/L) (median (Q1, Q3))*	9.6 (6.9, 13.2)	10.3 (7.4, 14.7)	0.59	9.6 (7.6, 13.2)	9.0 (7.1, 12.0)	0.09	9.5 (7.6, 11.5)	8.8 (6.9, 12.5)	0.28
Creatinine– (mg/dL) (median (Q1, Q3))*	0.9 (0.7, 1.6)	1.2 (0.8, 2.3)	0.03	0.9 (0.7, 1.3)	0.9 (0.7, 1.4)	0.99	1.0 (0.7, 1.3)	0.8 (0.7,1.3)	0.37
Creatinine– (µmol/L) (median (Q1, Q3))*	81 (58, 139)	104 (68, 200)	0.03	78 (63, 114)	81 (62, 124)	0.99	84 (61, 119)	74 (61, 114)	0.37
Bilirubin– (mg/dL) (median (Q1, Q3))*	0.88 (0.53, 2.14)	0.98 (0.56, 1.65)	0.94	0.85 (0.53, 1.45)	0.83 (0.53, 1.61)	0.98	0.80 (0.48, 1.61)	0.80 (0.51, 1.30)	0.85
Bilirubin– (µmol/L) (median (Q1, Q3))*	15.1 (9.0, 36.7)	16.7 (9.5, 28.3)	0.94	14.5 (9.1, 24.9)	14.2 (9.1, 27.5)	0.98	13.7 (8.2, 27.6)	13.7 (8.6, 22.3)	0.85
Platelet– (10^9/L) (median (Q1, Q3))*	153 (89, 245)	160 (92, 267)	0.51	178 (126, 251)	206 (159, 275)	0.01	209 (144, 259)	210 (157, 249)	0.93
INR– (median (Q1, Q3))*	1.3 (1.1, 1.5)	1.3 (1.1, 1.6)	0.53	1.2 (1.0, 1.3)	1.2 (1.1, 1.3)	0.58	1.1 (1.0, 1.3)	1.2 (1.1, 1.3)	0.47
C-reactive Protein– (mg/L) (mean±SD)†	161±81	163±82	0.85	139±80	133±82	0.62	96±71	80±62	0.10
Hemoglobin– (g/L) (mean±SD)	96.7±20.2	98.4±20.2	0.55	105.3±23.3	108.6±21.2	0.25	114.5±21.8	114.4±25.3	0.97
BMI– (kg/m^2) (median (Q1, Q3))*	27.1 (22.1, 32.8)	27.3 (24.2, 34.1)	0.17	27.2 (24.2, 32.9)	27.4 (23.4, 32.4)	0.55	26.9 (22.5, 32.5)	27.7 (23.7, 31.1)	0.76
Phosphate– (mmol/L) (mean±SD)†	0.93±0.43	1.00±0.47	0.20	0.92±0.43	0.95±0.40	0.64	0.97±0.49	0.96±0.40	0.93
Albumin– (g/L) (mean±SD)	25.6±5.1	25.4±5.3	0.73	29.0±8.6	29.3±4.6	0.78	31.0±5.6	31.3±4.9	0.68
Prealbumin– (g/L) (mean±SD)†	0.07±0.02	0.07±0.02	0.09	0.12±0.01	0.12±0.01	0.63	0.25±0.17	0.24±0.16	0.59
Transferrin– (g/L) (mean±SD)†	1.1±0.4	1.0±0.4	0.10	1.3±0.3	1.4±0.4	0.02	1.6±0.5	1.6±0.5	0.47
24 hours urinary urea nitrogen– (mmol/d) (median (Q1, Q3))*†	249 (125, 349)	203 (118, 346)	0.37	248 (156, 375)	269 (189, 410)	0.25	278 (205, 406)	274 (181, 412)	0.86
Nitrogen balance (g) (mean±SD)†	-4.8±5.4	-4.2±5.7	0.53	-4.9±5.6	-5.4±7.0	0.55	-6.0±6.6	-6.5±7.5	0.68
Time from eligibility to randomization– (hours) (median (Q1, Q3))*	0.6 (0.0, 12.0)	0.0 (0.0, 10.5)	0.67	0.0 (0.0, 10.0)	0.0 (0.0, 4.0)	0.59	1.0 (0.0, 8.0)	1.0 (0.0, 5.0)	0.63

APACHE II: Acute Physiology and Chronic Health Evaluation II; **SOFA**: Sequential Organ Failure Assessment; **INR:** International normalized ratio; **BMI**: Body mass index; SD: Standard deviation; Q: quartile

*Testing using Wilcoxon-Mann-Whitney test

†Data on laboratory values were not available for some patients; the numbers of patients with available data were as follows: C-reactive protein, 717 patients; prealbumin, 675 patients; transferrin, 720 patients; 24-hour urinary nitrogen excretion, 597 patients; phosphate, 854 patients; nitrogen balance, 596 patients.

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Table S2. Study interventions and co-interventions of patients stratified by prealbumin levels and randomized to permissive underfeeding and standard feeding.

Variable	Prealbumin ≤0.10 g/L N= 200			Prealbumin >0.10 and ≤0.15 g/L N=254			Prealbumin >0.15 g/L N=221		
	Permissive underfeeding N=98	Standard feeding N=102	P-value	Permissive underfeeding N=125	Standard feeding N=129	P-value	Permissive underfeeding N=111	Standard feeding N=110	P-value
Interventions									
Calculated caloric requirement– (kcal/day) (mean±SD)	1781±382	1803±305	0.65	1897±414	1874±433	0.66	1880±353	1861±374	0.70
tudy caloric target– (kcal/day) (mean±SD)	1029±250	1803±305	<0.0001	1126±252	1874±432	<0.0001	1110±249	1863±376	<0.0001
Achieved daily caloric intake– (kcal) (mean±SD)	840±261	1228±449	<0.0001	920±300	1353±451	<0.0001	850±317	1359±508	<0.0001
% of requirement achieved– (mean±SD)	47.4±11.3	68.2±21.9	<0.0001	48.9±13.0	73.2±20.3	<0.0001	45.7±15.7	73.8±23.7	<0.0001
Caloric source– (kcal) (mean±SD)									
Enteral	772±261	1156±442	<0.0001	830±307	1257±451	<0.0001	752±291	1265±528	<0.0001
Propofol*†	36.4±60.9	42.7±73.9	0.69	59.4±76.3	61.3±83.1	0.98	64.3±85.1	57.7±73.9	0.96
Dextrose*†	29.8±47.5	30.8±48.7	0.88	32.4±55.2	31.7±54.8	0.49	35.5±62.6	37.9±56.3	0.39
PN*†	2.2±21.5	0.0±0.0	0.31	0.04±0.41	4.9±54.1	1.0	2.7±22.8	5.4±53.7	0.60
Calculated protein requirement– (g/day) (mean±SD)	80.4±20.3	82.0±20.2	0.57	83.2±17.9	84.0±18.6	0.70	79.3±16.7	84.5±16.8	0.02
Achieved protein intake– (g/day) (mean±SD)	54.3±19.2	51.6±19.4	0.32	58.3±21.8	58.0±21.0	0.93	50.4±21.6	59.2±25.1	0.006
% of requirement achieved– (mean±SD)	69.3±21.6	64.6±23.6	0.14	70.1±22.6	70.1±21.9	0.98	64.4±25.1	70.9±26.8	0.07
Duration of intervention– (days) (mean±SD)	9.1±4.2	9.6±4.3	0.38	9.9±4.3	9.9±4.2	0.99	8.8±4.6	9.6±4.6	0.23
Co-interventions									
Received insulin– no. (%)	57 (58.2)	67 (65.7)	0.27	60 (48.0)	71 (55.0)	0.26	51 (46.0)	52 (47.3)	0.84
Daily insulin dose– (units) (median (Q1, Q3))*	3.6 (0.0, 21.5)	8.3 (0.0, 31.9)	0.15	0.0 (0.0, 18.5)	2.0 (0.0, 24.8)	0.16	0.0 (0.0, 22.0)	0.0 (0.0, 18.6)	0.92
Formulae– no. (%)									
Disease non-specific	40 (40.8)	30 (29.4)		77 (61.6)	74 (57.4)		70 (63.1)	66 (60.0)	
Disease specific	58 (59.2)	72 (70.6)	0.09	48 (38.4)	55 (42.6)	0.49	41 (36.9)	44 (40.0)	0.64

PN: Parenteral nutrition; **Disease-Non-Specific formula**: Osmolite, Jevity, Promote, Ensure plus, Resourse, Ensure, Resource plus, Jevity(1.2)
Disease Specific formula: Glucerna, Nutric hepatic, Nepro, Pulmocare, Novasource Renal, Peptamen(1.0), Peptamen(1.2), Suplena, Oxepa
*Testing using Wilcoxon-Mann-Whitney test.
†Calories from propofol, dextrose and PN are reported as means±SD although they are not normally distributed to be consistent with other variables related to calories which were normally distributed.

Table S3. Outcome data of patients stratified by prealbumin levels and randomized to permissive underfeeding and standard feeding. The association with different outcomes was adjusted to APACHE II score, creatinine level and sepsis and is reported as adjusted odds ratio (aOR) with 95% confidence intervals (CI).

Outcomes	Prealbumin ≤0.10 g/L N= 200				Prealbumin >0.10 and ≤0.15 g/L N=254				Prealbumin >0.15 g/L N=221				P-Value for inter-action
	Permissive underfeeding N=98	Standard feeding N=102	aOR or correlation coefficient (95% CI)	P-value	Permissive underfeeding N=125	Standard feeding N=129	aOR or correlation coefficient (95% CI)	P-value	Permissive underfeeding N=111	Standard feeding N=110	aOR or correlation coefficient (95% CI)	P-value	
28-day mortality– no. (%)	20/98 (20.4)	32/102 (31.4)	0.57 (0.30, 1.10)	0.09	19/124 (15.3)	18/129 (14.0)	1.19 (0.58, 2.42)	0.63	23/111 (20.7)	19/109 (17.4)	1.12 (0.56, 2.24)	0.74	0.10
90-day mortality– no. (%)	28/98 (28.6)	45/102 (44.1)	0.57 (0.31, 1.05)	0.07	23/124 (18.6)	30/128 (23.4)	0.79 (0.42, 1.48)	0.46	30/111 (27.0)	19/108 (17.6)	1.55 (0.80, 3.01)	0.20	0.01
180-day mortality– no. (%)	30/93 (32.3)	50/101 (49.5)	0.57 (0.31, 1.06)	0.08	25/124 (20.2)	32/127 (25.2)	0.79 (0.43, 1.45)	0.45	33/110 (30.0)	23/108 (21.3)	1.41 (0.75, 2.66)	0.28	0.01
ICU mortality– no. (%)	15/98 (15.3)	30/102 (29.4)	0.39 (0.19, 0.82)	0.01	14/125 (11.2)	16/129 (12.4)	0.95 (0.44, 2.06)	0.89	21/111 (18.9)	15/110 (13.6)	1.32 (0.63, 2.76)	0.46	0.02
Hospital mortality– no. (%)	22/97 (22.7)	45/102 (44.1)	0.33 (0.17, 0.65)	0.001	22/125 (17.6)	26/128 (20.3)	0.89 (0.47, 1.70)	0.73	32/111 (28.8)	22/110 (20.0)	1.37 (0.72, 2.61)	0.34	0.001
ICU length of stay– (days) (median (Q1, Q3))	14.0 (9.0, 18.0)	14.0 (8.0, 22.0)	-0.95 (-4.13, 2.22)	0.55	15.0 (9.0, 21.0)	15.0 (9.0, 25.0)	-2.02 (-4.84, 0.79)	0.16	12.0 (8.0, 19.0)	14.0 (9.0, 19.0)	-0.69 (-4.13, 2.76)	0.70	0.56
Hospital length of stay– (days) (median (Q1, Q3))	29.0 (17.0, 53.0)	28.0 (15.0, 46.0)	-1.5 (-19.9, 16.8)	0.87	37.0 (18.0, 75.0)	41.0 (17.0, 78.0)	-2.1 (-25.4, 21.2)	0.86	27.0 (17.0, 55.0)	41.5 (16.0, 83.0)	-17.8 (-35.00, -0.50)	0.04	0.25
Ventilation duration– (days) (median (Q1, Q3))	9.5 (5.0, 14.0)	11.0 (5.0, 17.0)	-1.98 (-4.67, 0.70)	0.15	11.0 (6.0, 16.0)	10.0 (6.0, 18.0)	-4.34 (-10.6, 1.98)	0.17	9.0 (6.0, 14.0)	10.0 (5.0, 14.0)	-0.07 (-2.73, 2.59)	0.96	0.42
PRBC transfusions– no. (%)	38/98 (38.8)	49/102 (48.0)	0.69 (0.39, 1.20)	0.19	44/125 (35.2)	32/129 (24.8)	1.70 (0.98, 2.95)	0.06	21/111 (18.9)	24/110 (21.8)	0.62 (0.30, 1.27)	0.19	0.77
Cumulative PRBC transfusion over 14 days– (units) (mean±SD)	0.16±0.44	0.18±0.27	-0.02 (-0.12, 0.08)	0.70	0.09±0.18	0.10±0.32	-0.01 (-0.06, 0.05)	0.86	0.06±0.17	0.07±0.24	-0.03 (-0.09, 0.02)	0.24	0.91
Hypoglycemia– no. (%)	3/98 (3.1)	2/102 (2.0)	1.58 (0.26, 9.66)	0.62	1/125 (0.8)	4/129 (3.1)	0.29 (0.03, 2.74)	0.28	0/111 (0.0)	1/110 (0.9)	NA	NA	NA
Hypokalemia– no. (%)	31/98 (31.6)	24/102 (23.5)	1.38 (0.73, 2.60)	0.32	32/125 (25.6)	26/129 (20.2)	1.48 (0.81, 2.70)	0.21	22/111 (19.8)	28/110 (25.5)	0.72 (0.38, 1.37)	0.32	0.12
Hypomagnesemia– no. (%)	28/98 (28.6)	32/102 (31.4)	0.88 (0.48, 1.60)	0.67	38/125 (30.4)	41/129 (31.8)	0.94 (0.55, 1.60)	0.81	38/111 (34.2)	36/110 (32.7)	1.07 (0.61, 1.87)	0.81	0.64
Hypophosphatemia– no. (%)	65/98 (66.3)	60/102 (58.8)	1.19 (0.66, 2.16)	0.57	90/125 (72.0)	86/129 (66.7)	1.26 (0.74, 2.16)	0.40	64/111 (57.7)	68/110 (61.8)	0.88 (0.51, 1.52)	0.64	0.36
Incident renal replacement therapy– no. (%)	9/86 (10.5)	18/87 (20.7)	0.48 (0.18, 1.28)	0.14	5/116 (4.3)	13/117 (11.1)	0.24 (0.06, 0.91)	0.04	9/101 (8.9)	5/103 (4.9)	2.24 (0.47, 10.62)	0.31	0.08
Healthcare-associated infections– no. (%)	33/98 (33.7)	44/102 (43.1)	0.67 (0.38, 1.19)	0.17	62/125 (49.6)	52/129 (40.3)	1.46 (0.89, 2.40)	0.14	42/111 (37.8)	43/110 (39.1)	1.0 (0.57, 1.74)	0.99	0.36
Urinary tract infection– no. (%)	14/98 (14.3)	13/102 (12.8)	1.14 (0.51, 2.57)	0.75	12/125 (9.6)	16/129 (12.4)	0.75 (0.34, 1.66)	0.48	12/111 (10.8)	9/110 (8.2)	1.36 (0.55, 3.37)	0.51	0.71
Catheter-related infection– no. (%)	2/98 (2.0)	4/102 (3.9)	0.51 (0.09, 2.85)	0.44	6/125 (4.8)	7/129 (5.4)	0.88 (0.29, 2.69)	0.82	2/111 (1.8)	3/110 (2.7)	0.66 (0.11, 3.99)	0.65	0.77
Ventilator associated pneumonia– no. (%)	12/98 (12.2)	22/102 (21.6)	0.51 (0.24, 1.09)	0.08	34/125 (27.2)	32/129 (24.8)	1.12 (0.64, 1.97)	0.69	24/111 (21.6)	25/110 (22.7)	1.06 (0.55, 2.04)	0.85	0.25
Severe sepsis or septic shock– no. (%)	0/98 (0.0)	0/102 (0.0)	NA	NA	1/125 (0.8)	0/129 (0.0)	NA	NA	0/111 (0.0)	1/110 (0.9)	NA	NA	NA
Feeding intolerance– no. (%)	14/98 (14.3)	21/102 (20.6)	0.70 (0.33, 1.48)	0.35	23/125 (18.4)	26/129 (20.2)	0.89 (0.48, 1.67)	0.72	18/111 (16.2)	21/110 (19.1)	0.82 (0.41, 1.64)	0.58	0.79
Diarrhea– no. (%)	23/98 (23.5)	40/102 (39.2)	0.42 (0.23, 0.80)	0.01	24/125 (19.2)	28/129 (21.7)	0.87 (0.47, 1.60)	0.65	23/111 (20.7)	23/110 (20.9)	0.82 (0.42, 1.63)	0.58	0.11

ICU: intensive care unit**; LOS:** length of stay; **PRBC**: Packed red blood cell; **NA**: not applicable;
Hypoglycemia: defined as blood glucose levels below 2.2 mmol/L; **Hypokalemia:** defined as drop in potassium to less than 2.8 mmol/L; **Hypomagnesemia**: defined as drop in magnesium to less than 0.60 mmol/L**;** **Hypophosphatemia**: defined as drop in phosphate to less than 0.70 mmol/L; **Feeding intolerance**: defined as vomiting, abdominal distention, or a gastric residual volume of more than 200 ml; **Diarrhea**: defined as three or more loose or liquid stools per day for 2 consecutive days.

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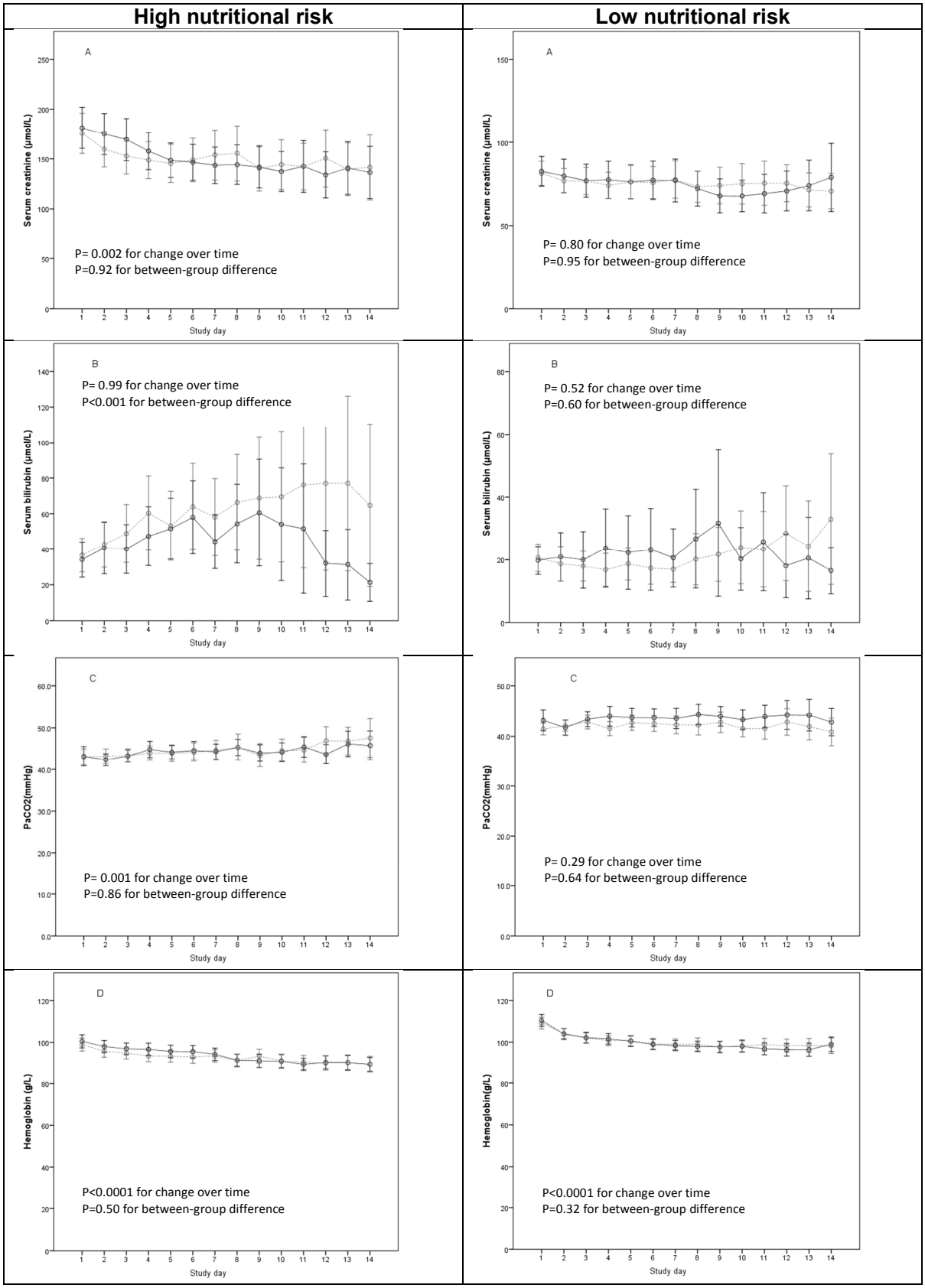
Figure legend

Figure S1. Daily serum creatinine, bilirubin, $PaCO_2$, hemoglobin levels, body weight, potassium, transferrin, and 24 hour urinary urea nitrogen in the permissive underfeeding and target feeding groups by the high nutritional risk (NUTRIC score 5-9) and low nutritional risk (NUTRIC score 0-4).



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