The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

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Summary

Background On the basis of low-quality evidence, international critical care nutrition guidelines recommend a wide range of protein doses. The effect of delivering high-dose protein during critical illness is unknown. We aimed to test the hypothesis that a higher dose of protein provided to critically ill patients would improve their clinical outcomes.

Methods This international, investigator-initiated, pragmatic, registry-based, single-blinded, randomised trial was undertaken in 85 intensive care units (ICUs) across 16 countries. We enrolled nutritionally high-risk adults (≥18 years) undergoing mechanical ventilation to compare prescribing high-dose protein (≥2·2 g/kg per day) with usual dose protein (≤1·2 g/kg per day) started within 96 h of ICU admission and continued for up to 28 days or death or transition to oral feeding. Participants were randomly allocated (1:1) to high-dose protein or usual dose protein, stratified by site. As site personnel were involved in both prescribing and delivering protein dose, it was not possible to blind clinicians, but patients were not made aware of the treatment assignment. The primary efficacy outcome was time-to-discharge-alive from hospital up to 60 days after ICU admission and the secondary outcome was 60-day morality. Patients were analysed in the group to which they were randomly assigned regardless of study compliance, although patients who dropped out of the study before receiving the study intervention were excluded. This study is registered with ClinicalTrials.gov, NCT03160547.

Findings Between Jan 17, 2018, and Dec 3, 2021, 1329 patients were randomised and 1301 (97·9%) were included in the analysis (645 in the high-dose protein group and 656 in usual dose group). By 60 days after randomisation, the cumulative incidence of alive hospital discharge was 46·1% (95 CI 42·0%–50·1%) in the high-dose compared with 50·2% (46·0%–54·3%) in the usual dose protein group (hazard ratio 0·91, 95% CI 0·77—1·07; p=0·27). The 60-day mortality rate was 34·6% (222 of 642) in the high dose protein group compared with 32·1% (208 of 648) in the usual dose protein group (relative risk 1·08, 95% CI 0·92–1·26). There appeared to be a subgroup effect with higher protein provision being particularly harmful in patients with acute kidney injury and higher organ failure scores at baseline.

Interpretation Delivery of higher doses of protein to mechanically ventilated critically ill patients did not improve the time-to-discharge-alive from hospital and might have worsened outcomes for patients with acute kidney injury and high organ failure scores.

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Introduction

Survival from critical illness has increased over the past three decades.[1] Survivors acquire protein-energy malnutrition with loss of muscle mass and associated worse clinical outcomes.[2] There is an argument to be made from basic physiological principles, animal studies, and clinical observations that protein could be the most important substrate to deliver in critically ill patients to maintain muscle mass and physical function and to improve clinical outcomes.[3,4] Labelled isotope studies suggest that exogenous amino acids could stimulate an anabolic response, yet other observational studies suggest benefits with both lower and higher protein doses in critically ill patients.[5,6] The few randomised trials evaluating different doses of protein have been limited by insufficient power or inconsistent adequate separation of protein dose between groups.[6] Consequently, the optimal protein dose during critical illness is unknown. Acknowledging the low amount of evidence, international critical care nutrition guidelines under expert opinion recommend a wide range of protein dose (1·2–2·0 g/kg per day), with even higher doses (2·0–2·5 g/kg per day) recommended for some subgroups of critically ill patients, such as people with obesity, burn patients, or patients with trauma.[7–11] Generating higher quality evidence to determine the efficacy of higher doses of protein

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Research in context

Evidence before this study

In our published systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and CINAHL Complete on April 1, 2021, using the search terms "critical illness", "critical care", "intensive care units", "proteins", "amino acids", and "peptides". We searched for randomised controlled trials of critically ill adult patients comparing higher versus lower protein with similar energy intake between groups and reported clinical or patient-centred outcomes, or both from database inception to April 1, 2021, with no language restrictions, and found 19 relevant publications. We also searched the reference lists of previous systematic reviews and personal files. We used the Canadian Critical Care Nutrition methodological quality scoring system (score range 1–14; higher score is better) and the Cochrane revised risk of bias (RoB2) to evaluate the quality of the included studies. We included 19 randomised controlled trials with 1731 patients (sample size range 14–474). The median Canadian Critical Care Nutrition score was 8, and only three studies had low risk of bias. Of the 11 studies that reported weight-based nutrition delivery, the pooled mean protein delivery between groups was 1·31 (SD 0·48) g/kg per day versus 0·90 (0·30) g/kg per day, whereas the pooled mean energy delivery between groups was 19·9 (SD 6·9) kcal/kg per day versus 20·1 (7·1) kcal/kg per day. Higher protein delivery versus lower protein delivery did not significantly affect overall mortality (risk ratio [RR] 0·91, 95% CI 0·75–1·10; p=0·34; heterogeneity I^2=0%) or other clinical or patient-centred outcomes. The published guidelines by the American Society for Parenteral and Enteral Nutrition (2016 and 2022) recommend a wide range of protein (1·2–2·0 g/kg per day) due to the paucity of trials with high-quality evidence, and no difference in clinical outcomes in the limited data.

Added value of this study

To our knowledge, this is the largest randomised controlled trial on protein dosing conducted in critically ill patients, focusing only on patients considered at high nutrition risk, and achieving a good separation of protein delivery between groups with similar energy delivery. Our results provide important evidence to guide protein dosing among critically ill patients.

Implications of all the available evidence

The results of this large-scale randomised controlled trial provide high-quality evidence against the efficacy of high dose protein and suggest that there might be a harmful effect in patients with acute kidney injury and high organ failure scores at admission. Future trials should focus on the identification of subcohorts of critically ill patients that could benefit from high-dose protein administration.

represents a top priority and a substantial challenge for the critical care community.[12]

In the past 20 years, we created a registry and clinicians voluntarily collected data on nutrition practices and outcomes from participating sites as part of an international quality improvement initiative.[13] In 2014, patients were prescribed, on average, 94 g of protein per day or approximately 1·3 g/kg per day (IQR 1·0–1·5 g/kg per day; range 0·5–3·8 g/kg per day).[14] Overall, patients treated at participating intensive care units (ICUs) received approximately 55% of prescribed protein requirements with site averages ranging from 15% to 101%. For the purpose of this trial, we converted this registry into a registry-based trial in which we aimed to test the hypothesis, in a cost-effective and pragmatic way, that delivery of a higher dose compared with the usual protein dose to mechanically ventilated adults with high nutritional risk would result in reduced time-to-discharge-alive from hospital.[15]

See Online for appendix

Methods

Study design

We conducted a large, international, investigator-initiated, pragmatic, registry-based, single-blinded, randomised trial in 85 ICUs across 15 countries (Argentina, Australia, Brazil, Canada, China, Greece, India, Iran, Japan, Malaysia, Mexico, Panama, Puerto Rico, Saudi Arabia, UK, and USA). The Effect of Higher Protein Dosing in Critically Ill Patients (The EFFORT Protein Trial) trial protocol has been published elsewhere.[16] All sites and personnel that participated in the data collection are listed in the appendix (pp 4–7).

The investigator-initiated trial protocol was approved by the Research Ethics Committees of Queen's University, Canada, and a central institutional review board at Vanderbilt University, TN, USA that granted a waiver of informed consent for sites that acceded to this central institutional review board. Otherwise, where required by local study sites, local ethics approval was obtained, and informed consent was also obtained from designated patient surrogates before randomisation.

Patients

We included adult patients (≥18 years) within 96 h of ICU admission who were expected to remain mechanically ventilated for at least 48 h from screening with one or more of the following nutritional risk factors: (1) low (≤25 kg/m²) or high (≥35 kg/m²) BMI;[17] (2) moderate to severe malnutrition, as defined by local assessments; (3) frailty, as defined by a Clinical Frailty Scale[18] of 5 or more from proxy; (4) sarcopenia, as defined by a SARC-F score[19] of 4 or more from proxy; and (5) from point of screening, projected duration of mechanical ventilation of more than 4 days.

We excluded patients who had received more than 96 continuous hours of mechanical ventilation before

screening, those expected to die or undergo withdrawal of life-sustaining treatments within 7 days from screening, pregnant women, patients for whom the responsible clinician felt that the patient either needed low or high protein (no clinical equipoise), and patients who required parenteral nutrition only in which the site did not have products to reach the high protein dose targets.

Randomisation and masking

Using random-sized permuted blocks of either 2, 4, or 8, a central randomisation system used a computer-generated randomisation schedule prepared by the study statistician stratified by site to allocate patients (1:1) to receive either high-dose protein or usual dose protein. Concealment of future treatment assignments was maintained using a secure, web-based randomisation system that was accessible to practitioners 24 h a day. As site personnel were involved in both prescribing and delivering protein dose, it was not possible to blind clinicians, but patients were not made aware of the treatment assignment.

Procedures

The assigned protein dose was commenced within 96 h of ICU admission or mechanical ventilation and as soon as possible after randomisation. The high-dose protein group was prescribed at least 2·2 g/kg per day or more compared with 1·2 g/kg per day or less for the usual dose group based on the upper and lower ranges of the American Society for Parenteral and Enteral Nutrition guidelines.[7,8] In both groups, protein targets were set using pre-ICU actual dry weight. For patients with a BMI above 30 kg/m², an ideal bodyweight based on a BMI of 25 kg/m² was used.

The trial did not control for total energy dose; however, clinicians were encouraged to avoid overfeeding energy and use published guidelines in both groups.[7,8] In the context of this pragmatic trial, we did not specify in the protocol how clinical teams achieved assigned protein goals, and the remainder of clinical care was at the discretion of ICU providers. Protein targets were achieved through any combination of enteral or parenteral nutrition, intravenous amino acids, or enteral protein supplements in both groups as per local standards of care. In both groups, clinicians were encouraged to achieve 80% of that which was prescribed.[20] The interventions were administered for up to 28 days, until death, or, until transition to full and permanent oral feeding. Patients re-admitted to the ICU within 28 days who required enteral or parenteral nutrition support continued with the previously assigned protein dose.

Outcomes

The original primary outcome for this trial was 60-day mortality and the secondary outcome was time-to-discharge-alive from hospital. We initially planned to enrol 4000 patients, which would achieve 80% power at a two-sided α of 0·05 to detect a 4% absolute risk reduction in 60-day mortality from 30% to 26%. Due to the COVID-19 pandemic, enrolment in this volunteer-driven, non-COVID-19 trial decreased substantially and achieving the original sample size was not feasible (appendix p 9). In June 11, 2021, after 42 months of enrolment and randomisation of 1100 patients, the Steering Committee considered switching the primary and secondary outcomes. Using the existing blinded dataset at that time to confirm pooled event rates, we estimated the pooled 60-day mortality rate to be 32% and a median time-to-

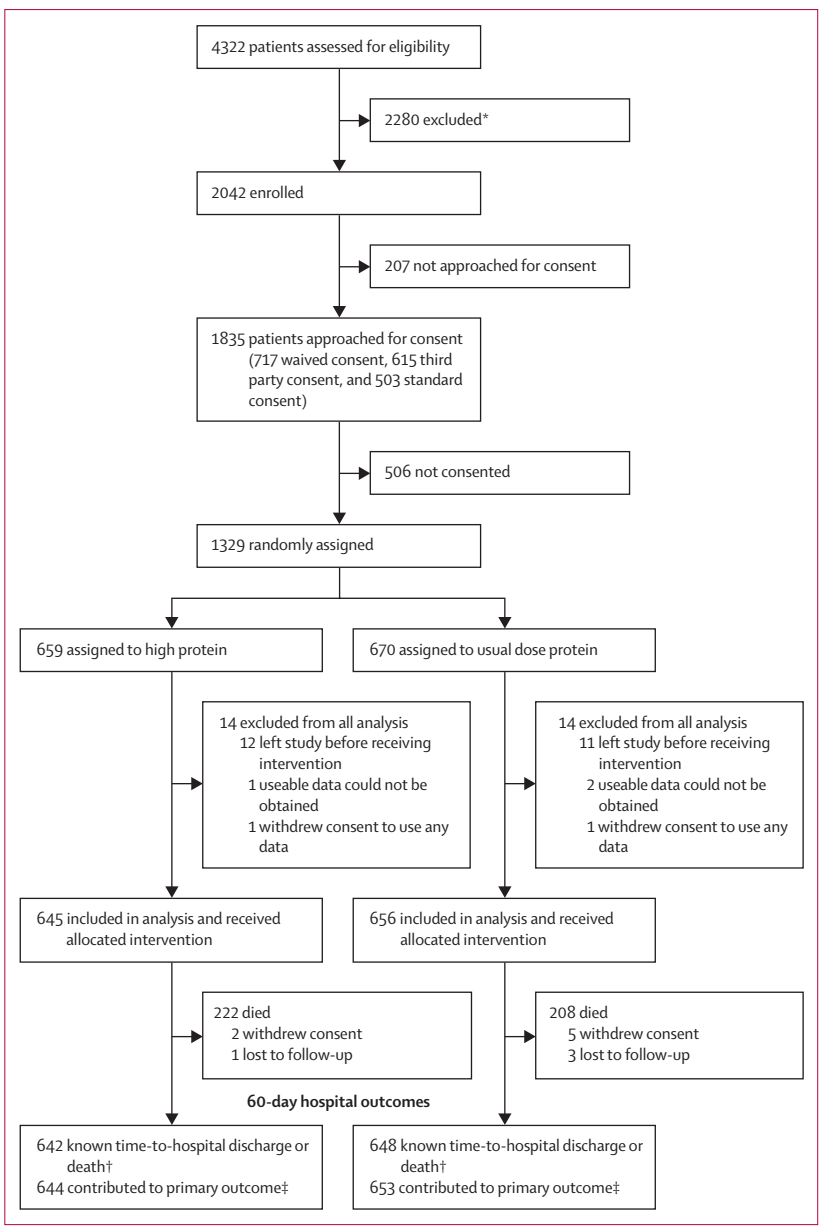

Figure 1: **Trial profile**
*One patient can be ineligible under more than one exclusion criteria. †All patients were censored if they remained in hospital at 60 days. ‡For the primary time-to-event analysis, patients who withdrew consent are censored at their time of consent withdrawal so all 1301 patients were used in the analysis except for four patients with missing hospital outcomes.

	High protein (n=645)	Usual dose protein (n=656)
Age, years	57 (17 [18–95])	57 (17 [18–93])
Sex		
Male	395 (61%)	388 (59%)
Female	250 (39%)	267 (41%)
Admission category		
Medical	548 (85%)	540 (82%)
Surgical elective	24 (4%)	19 (3%)
Surgical emergency	73 (11%)	97 (15%)
Primary ICU diagnosis		
Respiratory	275 (43%)	274 (42%)
Neurological	104 (16%)	93 (14%)
Sepsis	81 (13%)	90 (14%)
Trauma	59 (9%)	67 (10%)
Cardiovascular or vascular	56 (9%)	52 (8%)
Gastrointestinal	26 (4%)	37 (6%)
Other	23 (4%)	17 (3%)
Metabolical	13 (2%)	9 (1%)
Haematological	2 (<1%)	5 (<1%)
Burns	1 (<1%)	5 (<1%)
Orthopaedic	3 (<1%)	3 (<1%)
Renal	1 (<1%)	2 (<1%)
Gynaecological	1 (<1%)	2 (<1%)
COVID-19 positive on admission		
Yes	37 (6%)	48 (7%)
No	608 (94%)	608 (93%)
BMI	28 (10 [13–85])	28·6 (9 [13–77])
Pre-existing diabetes		
Yes	168 (26%)	161 (25%)
No	477 (74%)	495 (75%)
Charlson Comorbidity Index	1 (2 [0–11])	0·9 (2 [0–9])
Baseline SOFA score	9 (6–11)	9 (6–11)
Respiration	3 (2–4)	3 (2–4)
Coagulation	0 (0–0)	0 (0–1)
Liver	0 (0–1)	0 (0–1)
Cardiovascular	3 (0–4)	3 (0–4)
Central Nervous System	3 (1–4)	3 (0–4)
Renal	0 (0–1)	0 (0–1)
Use of vasopressor	254 (39%)	266 (41%)
APACHE II score	609/645 (21 [16–27])	621/656 (21 [15–26])
mNUTRIC score	609/645 (5 [3–6])	621/656 (5 [3–6])
Frailty	594/645 (3 [2–5])	601/656 (3 [2–4])
SARC-F score	583/645 (1 [0–5])	584/656 (1 [0–4])
Geographical region		
Canada	82 (13%)	85 (13%)
Australia and New Zealand	8 (1%)	10 (2%)
USA	110 (17%)	119 (18%)
UK	152 (24%)	157 (24%)
Europe	16 (3%)	15 (2%)
Latin America	151 (23%)	147 (22%)
Asia	126 (20%)	123 (19%)

(Table continues on next page)

discharge-alive from hospital among survivors of 21 days. On the basis of 1000 simulations using the aforementioned assumptions and assuming time-to-discharge-alive among survivors followed an exponential distribution, we estimated that a sample size of 600 patients per group would achieve 83% power at a two-sided α of 0·05 if there was a 15% relative risk reduction in hospital mortality from 34·6% to 29·5%, combined with a 20% increase in the hazard rate of time-to-discharge-alive among hospital survivors (appendix pp 29–34). Accordingly, with an expectation that the COVID-19 pandemic would persist and the trial would enrol at least 1200 patients to test the new primary outcome of time-to-discharge-alive from hospital, trial enrolment was set to end on Dec 3, 2021.

The revised secondary outcome was 60-day mortality. Tertiary outcomes include nutritional adequacy, hospital mortality, re-admission to ICU and hospital, duration of mechanical ventilation, and length (days) of ICU and hospital stay. All outcomes were assessed while in the hospital and up to a maximum of 60 days after admission except daily nutrition, which was assessed for the first 12 days in the ICU, and protein intake, which was assessed for the first 28 days after randomisation.

Statistical analysis

The primary outcome of time-to-discharge-alive from hospital was measured from randomisation to 60 days after initial ICU admission. Death was a competing risk, and patients who died within 60 days of ICU admission were considered to have never been discharged alive regardless of previous hospital discharge. For patients re-admitted to the index hospital within 60 days of the initial admission, we used the discharge information from the final recorded hospitalisation. For the primary analysis, the unadjusted cumulative incidence function curves are reported by group. The groups are compared by the sub-distribution hazard ratio for competing risks using the Fine-Gray[21] approach based the Cox proportional hazard model. In accordance with the statistical analysis plan, we also report the unadjusted Gray's test[22] and the sub-distribution hazard ratios based on the following adjusted models: (1) stratified by site; (2) adjusted for site as a random frailty;[23] and (3) adjusted for random site and the prespecified baseline covariates of age, APACHE II score, mNUTRIC score, clinical frailty score, sarcopenia (SARC-F), and admission type and geographical region, for which all continuous covariates were modelled as linear.

60-day mortality was compared between groups by unadjusted relative risks (RRs), Mantel-Haenszel site-stratified RRs, and adjusted RRs estimated by the mixed log-binomial model using Laplace estimation with site as a random effect and baseline covariates as fixed effects. Due to convergence issues, we excluded the mNUTRIC score from the log-binomial model. However, we also estimated RRs from a modified Poisson model using robust standard errors, which included all pre-selected covariates.

The tertiary outcomes are presented by treatment group using unadjusted descriptive statistics. Prespecified subgroup analyses were performed by baseline mNUTRIC score[24] (0–4 *vs* 5–9); BMI of more than 30 kg/m²; trauma; sepsis; acute kidney injury using Kidney Disease Improving Global Outcomes classification;[25] and age, APACHE II score,[26] and sepsis-related organ failure assessment (SOFA) score,[27] each broken at median value. The statistical significance of effect modification for time-to-discharge-alive from hospital was assessed by testing a treatment by covariate interaction term using the log-binomial model with random-site effect for mortality and Fine-Gray competing risk Cox regression with random-site frailty. Although we considered a two-sided p value of 0·05 or less as suggesting statistically significant effect modification, we acknowledge both limited power and the possibility of type 1 errors due to multiplicity of testing.

Patients were analysed in the group to which they were randomly assigned regardless of study compliance, except patients who dropped out of the study before receiving the study intervention (defined as receiving <24 h of after post randomisation) were excluded. The analysis was performed using SAS (version 9.4). Further details are included in the appendix (pp 17–34), which was posted to ClinicalTrials.gov, NCT03160547, before analysing outcomes by group. The study was monitored by an independent data safety monitoring board, but no interim analysis with formal stopping rules was conducted.

Role of the funding source

There was no funding source for this study.

Results

Between Jan 17, 2018, and Dec 3, 2021, 1329 patients were randomly assigned from 85 ICUs across 16 countries. Due to early death, discharge, or withdrawal of consent, 28 (2·1%) patients did not receive the assigned intervention and were excluded from the analysis. The primary modified intention-to-treat analysis includes 1301 (97·9%) patients (645 assigned to the high-dose protein group and 656 to the usual dose protein group; figure 1). For the primary time-to-event analysis, patients who withdrew consent were censored at their time of consent withdrawal and, due to four patients having missing hospital outcomes, 1297 patients were included in the primary analysis.

Baseline patient characteristics by group are outlined in the table, and the appendix (p 10) describes the characteristics of the sites participating in this trial.

Following randomisation, patients in the high-dose group were prescribed a mean of 2·2 (SD 0·1) g/kg per day protein compared with 1·2 (0·1) g/kg per day in the usual dose group. Patients in the high-dose group received a mean of 1·6 (SD 0·5) g/kg per day protein compared with 0·9 (0·3) g/kg per day in the usual dose group (appendix p 14). Both groups received a similar energy intake (14·7 [SD 6·9] kcal/kg per day *vs* 13·2 [6·4] kcal/kg per day). Daily amounts of protein and energy received by each group after randomisation are shown in figures 2 and 3. See the appendix (p 11) for other parameters related to protocol adherence.

	High protein (n=645)	Usual dose protein (n=656)
(Continued from previous page)		
Unintentional weight loss before admission to hospital		
Yes	94 (15%)	100 (15%)
No	381 (59%)	395 (60%)
Unknown	170 (26%)	161 (25%)
Bodyweight lost (%)	94/645 (13%); 10 (2–50)	100/656 (12%; 9 (1–37)
Months of weight loss before admission to hospital	94/645 (5%); 4 (1–13)	100/656 (4%); 3 (1–13)
Decreased food intake before admission to hospital		
Yes	137 (21%)	168 (26%)
No	337 (52%)	327 (50%)
Do not know	171 (27%)	160 (24%)
Missing	0 (0%)	1 (<1%)
Food intake <50% of needs before hospital admission		
Yes	93/645 (14%)	119/656 (18%)
No	552/645 (86%)	537/656 (82%)
Chronic malabsorption on hospital admission		
Yes	10 (2%)	11 (2%)
No	559 (87%)	571 (87%)
Do not know	76 (12%)	73 (11%)
Missing	0 (0%)	1 (<1%)
Moderate or severe fat or muscle wasting on hospital admission		
Yes	119 (18%)	113 (17%)
No	406 (63%)	438 (67%)
Do not know	116 (18%)	102 (16%)
Missing	4 (1%)	3 (1%)
Renal replacement therapy on randomisation day		
Yes	77 (12%)	58 (9%)
Acute kidney injury at time of randomisation*		
Yes	163 (25%)	149 (23%)
Stage 1	59 (9%)	61 (9%)
Stage 2	43 (7%)	31 (5%)
Stage 3	61 (10%)	57 (9%)
Moderate or severe chronic renal disease†		
Yes	63 (10%)	54 (8%)
No	582 (90%)	602 (92%)
Moderate or severe chronic liver disease‡		
Yes	17 (3%)	11 (2%)
No	628 (97%)	645 (98%)

Data are n (%), mean (SD), or median (IQR), unless otherwise indicated. APACHE=Acute Physiology and Chronic Health Evaluation. ICU=intensive care unit. SOFA=Sequential Organ Failure Assessment. mNUTRIC=modified Nutrition Risk Assessment in Critical Illness Score. *Acute kidney injury refers to patients who met the criteria of KDIGO: stage 1 is at least 26·52 μmol/L increase in serum creatinine from baseline within 48 h or 1·5–1·9 times baseline within 7 days; stage 2 is 2·0–2·9 times baseline within 7 days; stage 3 is three times or more baseline within 7 days or increase to at least 353·6 μmol/L with an acute increase of more than 44·2 μmol/L. †Defined in comorbidities as moderate renal disease: creatinine clearance 51–85 mL/min; and severe renal disease: creatinine clearance less than 50 mL/min and not on dialysis. ‡Defined in comorbidities as mild liver disease: raised serum aminotransferase or alkaline phosphatase levels or both, but total serum bilirubin less than 2·5 mg/dL and no coagulopathy (international normalised ratio <1·5); and moderate or severe liver disease: liver disease beyond the above definition for mild liver disease.

Table: **Baseline characteristics of the primary modified intention-to-treat analysis**

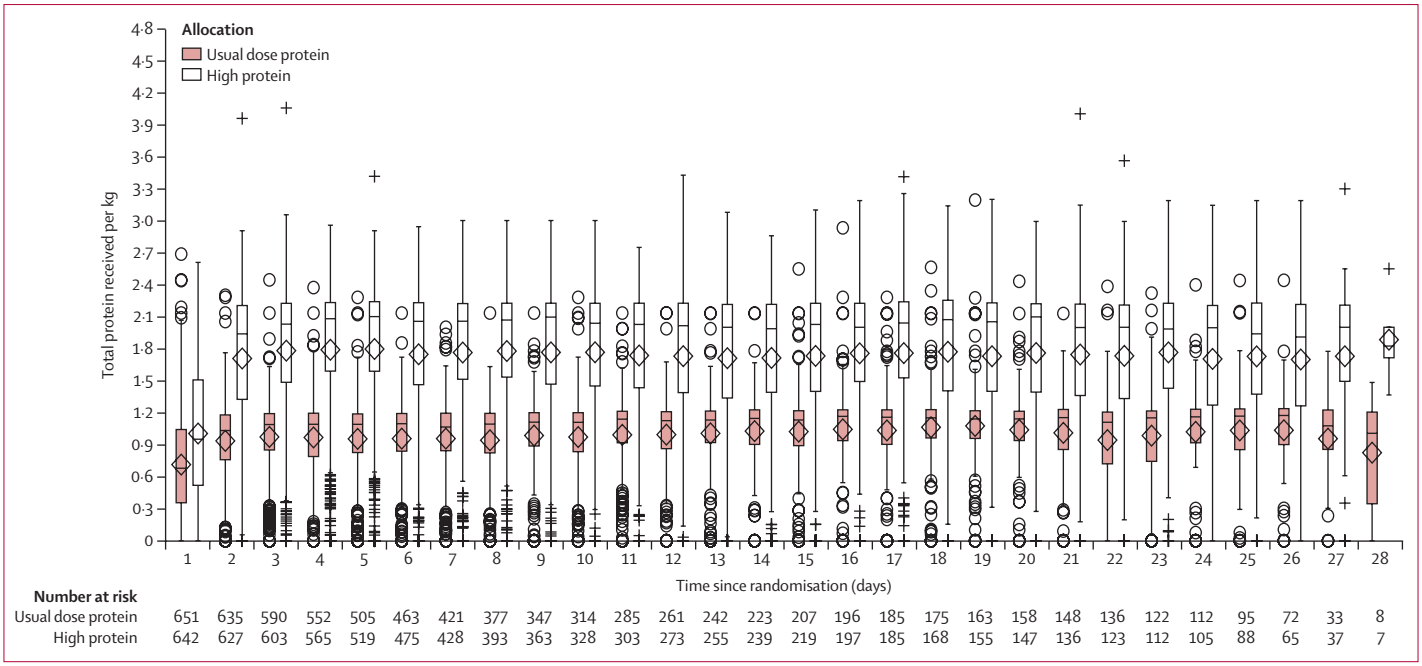

Figure 2: **Protein received in the first 28 days after randomisation**

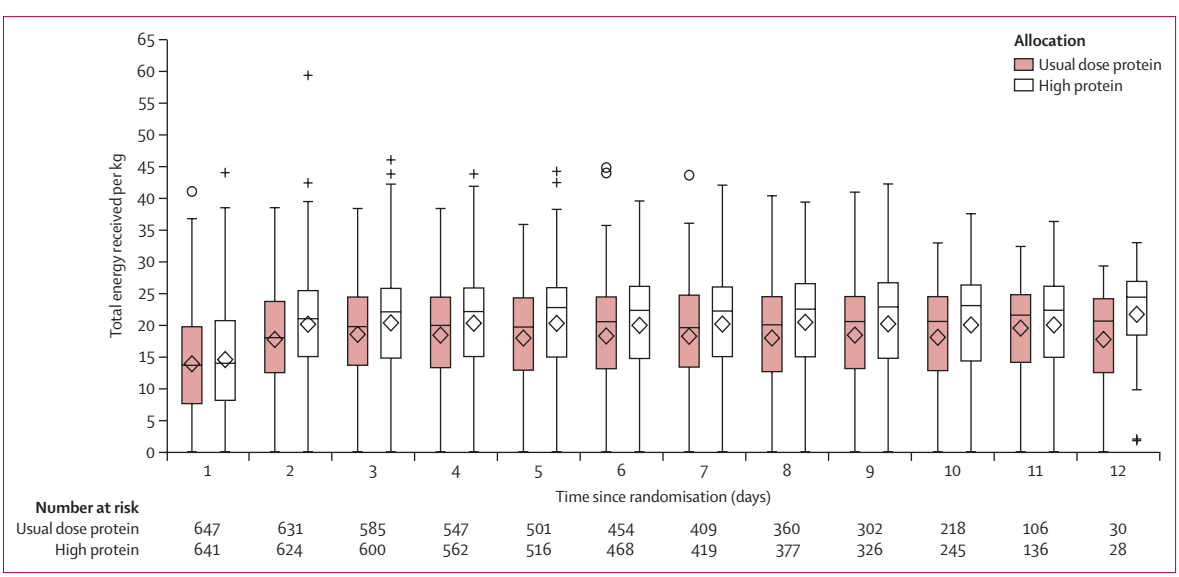

Figure 3: **Energy received for the first 12 days after randomisation**

By 60 days after randomisation, the cumulative incidence of alive hospital discharge was 46·1% (95 CI 42·0%–50·1%) in the high-dose protein group compared with 50·2% (46·0%–54·3%) in the usual dose protein group (HR 0·91, 95% CI 0·77–1·07; p=0·27; figure 4). We found no evidence of difference in time-to-discharge-alive between study groups even after adjusting for sites and covariates (appendix p 12). The 60-day mortality rate was 34·6% (222 of 642) in the high-dose protein group compared with 32·1% (208 of 648) in the usual dose protein group (RR 1·08, 95% CI 0·92–1·26; appendix p 12). Hospital mortality, duration of mechanical ventilation, ICU stay, and hospital stay were similar between groups (appendix p 13).

Subgroup analysis suggested an interaction between protein dose and patients with acute kidney injury (stage 1–3) and high SOFA score (≥9) upon admission on both time-to-discharge-alive (appendix p 15) and 60-day mortality (appendix p 16), favouring the usual protein dose.

During the study period, patients who received high-dose protein as compared with usual dose protein had a higher urea concentration by 2·1 mmol/L

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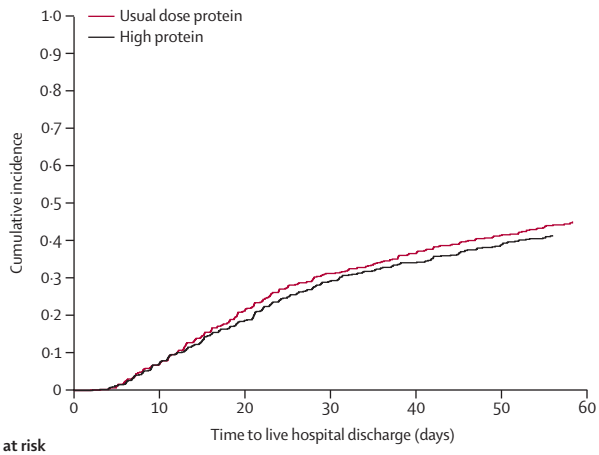
(14·0 [SD 8·5] mmol/L *vs* 11·9 [7·2] mmol/L). There were no clinically important differences in other metabolic parameters between groups (appendix p 13).

Discussion

We conducted a large, international, investigator-initiated, pragmatic, registry-based, single-blinded, randomised trial to compare high protein dose versus usual protein dose in critically ill patients. To conduct this trial, we partnered with nutrition practitioners worldwide and randomly assigned the patients to receive either a higher dose of protein or usual dose. Although most patients received reasonable amounts of energy, there was variability in the amounts of energy patients received in both groups. Compared with other trials of protein dosing,[28] we achieved reasonable between-group separation of actual protein dose delivered (a difference of 0·7 g/kg per day), but despite this difference, there were no between-group differences in time-to-discharge-alive or 60-day mortality. Subgroup analyses suggested that high protein in patients with greater severity of illness and those with acute kidney injury at ICU admission could be harmful.

Despite an overall null finding, our trial results will affect practice guidelines worldwide. Our findings do not support the prevailing notion that mechanically ventilated patients who are older, obese, more severely ill, frail, malnourished, or sarcopenic benefit from a higher protein dose. In contrast, higher protein dosing could be harmful in patients with greater severity of illness (as judged by baseline SOFA score and presence of acute kidney injury). These subgroup findings are consistent with a post-hoc analysis of a multicentre trial evaluating the effect of artificial nutrition support in hospitalised patients, which found no associated benefit of nutrition in patients with an elevated C-reactive protein, despite finding a positive treatment effect in patients who have less inflammation.[29] Furthermore, the interaction between higher amino acid or protein intake, baseline kidney injury, and worse clinical outcomes has been observed in two other post-hoc analyses from prospective randomised trials evaluating high protein or amino acid intake.[30,31] The test for interaction in this subgroup analysis (p=0·001 for time-to-discharge alive and p=0·02 for 60-day mortality) suggests that chance is an unlikely explanation. The fact that the high-dose protein group experienced increased ureagenesis could suggest that patients with acute kidney injury, coupled with impaired muscle protein synthesis, have a metabolic burden due to excessive protein-amino acid breakdown. We caution clinicians not to use high protein doses in patients with acute kidney injury and multiple organ failure (high SOFA scores).

On the basis of observational and sparse randomised trial data, current critical care nutrition guidelines recommend higher protein dose for critically ill patients with obesity.[6] In our trial, the benefit of higher protein on time-to-discharge-alive in the more than a third of enrolled patients with obesity was not observed (HR 0·80, 95% CI 0·60–1·1), which rules out any clinically important positive treatment effect. Our trial enrolled a too low number of surgical, trauma, or burn patients to answer the question of protein dosing in these populations. However, the overall null findings combined with the possibility of harm in patients with greater severity of illness does not support current recommendations that suggest that these patients require much higher doses of protein (≥2·0 g/kg per day). More research is required to determine the optimal protein dose in other types of critically ill patients such as surgical, burn, and trauma patients, and people with obesity.



Number at risk							
Deaths (high dose protein)	..	95	162	184	207	218	222
Deaths (usual protein)	..	91	142	175	185	198	208
Hospitalisation (high protein)	644	499	353	261	204	165	144
Hospitalisation (usual dose protein)	653	513	364	261	216	175	145

Figure 4: **Time-to-discharge-alive from hospital by treatment group**
The figure shows the cumulative incidence of time-to-discharge-alive from hospital (primary outcome) by treatment group. Overall estimate of treatment effect: HR 0·91, 95% CI 0·77–1·07; p=0·27.

In contrast to our a-priori hypothesis, the mNUTRIC score (or other measures of malnutrition) did not identify patients who benefit the most from high protein dosing. In fact, we observed a trend towards the opposite, that patients with a low mNUTRIC score might benefit from higher protein intake compared with high-mNUTRIC patients (test for interaction, p=0·10). This finding is internally consistent given that mNUTRIC is made up of APACHE II and SOFA scores and strengthens the inference that patients with greater severity of organ dysfuction do not benefit from high protein dosing.

The strengths of our trial include the large and diverse sample size from multiple practice settings, all of which enhance the generalisability of our findings. We acknowledge several limitations. First, study staff and clinicians were not blinded; due to the nature of the study, they were expected to influence the subsequent nutrition care of enrolled patients. However, the allocation of treatment assignment was concealed, study endpoints

were objectively defined, loss to follow-up was less than 1%, and 97% of randomly assigned patients were included with known primary and secondary outcomes, all of which enhance the validity of the results. Second, due to extenuating COVID-19 circumstances, we reduced our planned sample size and switched our primary and secondary outcomes. Consequently, our trial is underpowered with respect to 60-day mortality. Nevertheless, the upper end of the 95% CI on time-to-discharge-alive from hospital preclude all but a small treatment benefit (95% CI 0·77–1·07). Third, we did not collect functional, performance-based, or longer-term outcome measures. Higher protein dose in critically ill patients might not affect mortality or length of hospital stay, but it remains unknown whether higher protein improves the physical recovery of survivors of critical illness, especially when protein is administered with exercise.[28,32] Fourth, our trial did not consider the theoretical phases of critical illness and administered the same dose throughout the 28-day study period. The precise definitions of these phases and when one patient transitions to another phase is currently not well described. However, future trials evaluating higher protein dose starting later during the ICU stay, when patients are more likely to be anabolic, are warranted.[33] Fifth, consistent with other large-scale pragmatic nutrition trials, we observed considerable within-group variation in nutrition intake. Nevertheless, we did maintain reasonable overall separation in protein intake between groups. Although variation in protein intake could attenuate the signal of benefit (or harm) compared with all patients receiving their protein target, we believe the real-world practice context of this trial is a strength because it improves generalisation to a realistic implementation of the two intended protein targets. Finally, we acknowledge that time-to-discharge-alive can be a problematic endpoint in unblinded trials, such as this trial, in as much as unblinded clinicians can influence the timing of discharge and therefore exert a bias on the trial results. However, it is likely that most participating clinicians had a bias favouring the use of high protein and despite this potential bias, we did not see a beneficial treatment effect of high protein dosing. An ongoing blinded multicentre trial of different protein doses could show any effect that blinding might have had on our study results.[34]

In conclusion, prescribing 1·2 g/kg per day (lower end of the American Society for Parenteral and Enteral Nutrition 2022 guidelines[8] or 1·3 g/kg per day to be consistent with the European Society of Parenteral and Enteral Nutrition 2019 guidelines[9]) and striving to achieve 80% of what was prescribed seems like a reasonable and safe approach for all critically ill patients. Delivering higher doses of protein to critically ill patients did not improve the time-to-discharge-alive from hospital compared with usual dose protein and might have worsened outcomes for patients with acute kidney injury and greater severity of illness. Delineating which subgroups of critically ill patients (eg, those with burns, trauma, obesity, or recovering from surgery) that could benefit from higher doses of protein requires more research to define the optimal dose and timing of administration.

Contributions

This investigator-initiated trial was designed by DKH (the sponsor of the trial) and AGD (the study statistician) in consultation with the EFFORT Protein Trial Steering Committee. AGD supervised XJ, who conducted the analysis. DKH and CC conceptualised the study. DKH, CC, TWR, JP, DEB, CS, LO-R, and AGD developed the methods. JP, CC, TWR, DEB, Z-YL, VCG, KO, RR, CW, and MI-E collected the data. AGD and XJ accessed and verified all data analysis and produced the manuscript figures and tables. DKH wrote the original draft of the paper. DKH and the writing committee wrote the manuscript. JP, CC, TWR, DEB, Z-YL, VCG, KO, RR, CW, MI-E, CS, LO-R, XJ, and AGD reviewed and edited the drafts of the paper. All authors had final responsibility for the decision to submit for publication. Collectively, the Steering Committee vouches for the data, the analysis, and the decision to publish the data. No core funding was received for the EFFORT Protein trial.

Declaration of interests

The UK sites received support in the form of protein supplement supply from Nutrinovo (prosource tube feed [TF]) and Stanningly Pharma (Renapro Shot), and CA$20 000 from Nutricia to cover insurance and project management costs locally. Those that provided financial and product support for the trial had no role in designing the protocol, conducting the trial, or analysing the data, and did not have access to the data nor influence the content of the publication. We declare no competing interests.

Data sharing

Data collected for this study will not be publicly available but are being used internally for secondary purposes. Data dictionary or other study tools are available from the corresponding author upon request.

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