# The Association of Enteral Protein Intake with Outcomes in Trauma ICU Patients

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A thesis
submitted in partial fulfillment of the
requirements for the degree of
Master of Science
University of Washington
2025

Committee:
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Program Authorized to Offer Degree:
Department of Epidemiology

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## Abstract

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Critically ill trauma patients have distinct nutritional requirements due to increased catabolism and metabolic stress. Existing nutrition guidelines provide limited and outdated recommendations on optimal protein intake for this population. Recent studies suggest a potential dose-dependent harm associated with high protein intake in critically ill patients. We conducted a secondary analysis of a randomized clinical trial to investigate the relationship between early protein intake and ventilator-free days (VFDs), and to assess whether blood urea nitrogen (BUN)—a known marker of poor outcomes in ICU patients—mediates this relationship.

This analysis included 329 trauma patients from a single-center randomized trial conducted between 2016 and 2021 at a Level 1 trauma center. The primary exposure was mean protein intake (g/kg/day) over the first week of ICU admission. The primary clinical outcome was VFDs, defined as days alive and free from mechanical ventilation within the first 28 days. Competing risks regression was used to analyze VFDs to calculate the subdistribution hazard of extubation, accounting for death as a competing event. A causal mediation analysis evaluated whether BUN mediated the relationship between protein intake and VFDs. The association between protein intake and secondary outcomes including acute respiratory distress syndrome (ARDS), ventilator-associated pneumonia (VAP), and aspiration were analyzed using logistic regression. Sensitivity analyses were performed for a subgroup of patients receiving ≥8kcal/kg/day.

Median patient age was 46 years (IQR: 30–59), 78% were male, and median injury severity score (ISS) was 34 (IQR: 26–43). Median protein intake was 1.6 g/kg/day (IQR: 1.0–2.0). Median VFDs was 14 (IQR 0–20). Each 1 g/kg/day of protein intake in the first week of ICU stay was associated with a significantly lower hazard of extubation (SHR 0.66; 95% CI: 0.53 to 0.81; p<0.001). Secondary outcomes, including ARDS, VAP, and aspiration, showed no significant associations with protein intake. Causal mediation analysis indicated that each additional 1 g/kg/day protein intake resulted in 3.53 fewer VFDs (95% CI: –4.81 to –2.30; p<0.001), with approximately 26% (95% CI: 12.0% to 41.0%) mediated by elevated BUN levels.

In critically ill trauma patients, higher enteral protein intake early in ICU admission was associated with a lower hazard of extubation and fewer VFDs, partly due to elevations in BUN. These findings challenge current recommendations advocating high protein supplementation in trauma patients and highlight the need for further trials to define optimal protein dosing strategies tailored specifically to this high-risk population.

## Introduction:

Nutritional care in critically ill patients has benefited from several randomized clinical trials addressing timing and mode of nutritional intake[1-4.] However, trauma patients are frequently underrepresented in these studies, sometimes comprising as low as 2% of the study subjects[2-4]. This limits our ability to develop robust, evidence-based practice recommendations for this group of patients. Critically ill trauma patients are uniquely susceptible to increased catabolism and impaired immune function due to the additional stress of repeated surgical procedures. Despite this, optimal protein intake for this population remains debated, and existing guidelines have not been substantially updated since 2016 because of limited robust trials.

Current American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines provide only weak evidence to support specific protein recommendations in both medical and surgical intensive care unit (ICU) patients.[5] Recent comparisons of nutrition trials also indicate that protein intake may follow a curvilinear relationship with mortality—suggesting that there is an optimal amount that can be administered before the risk of mortality outweighs the benefit of protein intake in the acute period.[6] This dose-dependent harm of protein-intake on outcomes is under investigation and is pertinent to the critically ill trauma population as current guidelines suggest that these patients, in addition to burn and obese patients, might benefit from more than 2.5 g/kg/day of protein in the critical care setting.

In our previous single-center randomized trial, critically ill surgical and trauma patients were assigned to either standard enteral nutritional support or standard enteral nutrition plus enteral protein supplementation to a target of 2 g/kg/day. Subjects were followed until hospital discharge, and the primary clinical outcome was ventilator-free days (VFDs). We observed non-statistically significant fewer VFDs in the supplemental protein arm, and no other differences in clinical outcomes. Moreover, there was a wide range of protein intake across all study subjects over the first week of nutritional support. This overlap was not unexpected and provided the opportunity to evaluate a range of overall protein intake, which can lend more insight into the relationship between protein intake and outcomes.

We performed a secondary analysis focusing on the trauma patients who were enrolled in the clinical trial. We first tested the hypothesis that protein intake was associated with extubation timing. Second, we sought to determine whether blood urea nitrogen (BUN) mediated this relationship, potentially offering insight into the underlying physiological mechanisms. BUN has been previously identified as a predictor of long-term mortality in critically ill patients and this study aimed to explore its role as a mediator in the relationship between protein intake and outcomes in trauma patients requiring nutritional support.[7]

## Methods

### *Study Design, Setting, and Participants*

Between November 2016 and November 2021, 500 patients were enrolled (ClinicalTrials.gov ID: NCT03170401) at a Level 1 trauma center in the United States. As described above, subjects were randomized to either a standard enteral nutritional support group or to treatment with supplemental enteral protein. Patients were screened and considered for inclusion if they were receiving mechanical ventilation, expected to require ICU care for at least 7 days, deemed ready to start enteral nutritional support within 24 – 72 hours of admission, and had no contraindications to full enteral support. Patients were excluded if they had severe chronic liver disease, chronic kidney disease, metastatic cancer, or were expected to die due to the severity of their illness or injuries. Additional details about design and conduct of the clinical trial and overall approach to clinical care are available in the supplemental material. For this study, we limited our analyses to the trauma patients who remained in the ICU for 7 days or greater.

### *Primary Exposure and Clinical Endpoints*

The primary independent variable was mean protein intake in grams per kilogram per day (g/kg/day) in the first week of feeding. Enteral nutrition began on the day the subject was randomized to the initial clinical trial and was less than 3 days after ICU admission. Intake was recorded prospectively daily using standardized protocols in the original trial. Mean protein intake per day was calculated by summing the daily enteral protein intake (in grams per kilogram) over the first seven days of enteral nutrition and dividing the total by seven.

The primary clinical endpoint of interest was VFDs, which is a validated composite marker of recovery from acute respiratory failure that also considers mortality. VFDs were defined as the total number of days that a patient was both alive and off mechanical ventilation within the first 28 days after ICU admission, starting from day 1 of admission to the ICU. Because VFDs combines two interrelated events—extubation and survival—we used competing-risks regression (Fine–Gray model) to directly model the subdistribution hazard of successful extubation, treating death before extubation as a competing event. Secondary outcomes were respiratory complications including development of acute respiratory distress syndrome (ARDS), ventilator-associated pneumonia (VAP), and adjudicated aspiration.

Missingness in demographic and covariate variables was under 10%. We retained all participants in the analyses using available-case data for each variable and imputation was not required. We conducted a sensitivity analysis that was limited to subjects who received greater than or equal to 8 kcal/kg/day from their enteral formula during the first 7 days of nutritional support. This excluded subjects who, for any reason, received substantially less than their prescribed nutritional intake.

### *Data Analysis*

Descriptive analyses were done to summarize patient demographics, baseline characteristics and outcomes. Continuous data were summarized as the median with 25th and 75th percentiles. Categorical data were summarized as counts with percentages.

VFDs were analyzed as time to successful extubation using Fine and Gray competing risk regression, with death as a competing event.[8-10] Successful extubation was defined as extubation greater than 48 hours without reintubation in a 28-day survivor. Patients who died before day 28 or before extubation received a VFD score of 0 to penalize non-survival, regardless of intubation status.[10] Patients were thus censored after day 28. This approach calculated the subdistribution hazard ratio (SHR) for time to successful extubation by protein intake and allowed for appropriate adjustment of chosen covariates. The results are reported as SHR with 95% confidence intervals and corresponding p-values. In addition to the composite outcome, the components of VFDs—28-day mortality and ventilator duration among 28-day survivors—were reported separately.

Nonlinearity of the association between protein and successful extubation was examined by incorporating a squared term for protein intake into the model. After comparing linear and nonlinear competing risks models using Akaike Information Criterion (AIC) scores, we found no improvement in model fit with the addition of the squared term. Therefore, we proceeded with the linear model for this study. Binomial logistic regression was done to analyze secondary outcomes.

Prespecified covariates in both the Fine-Gray and logistic regression models included age, injury severity score (ISS) in three categories (0-10: Mild, 10-25: Moderate, 25+: severe), and APACHE II score. These covariates were chosen based on baseline factors understood to influence outcomes after traumatic injury that may confound the relationship between protein intake and extubation.[11-13]

To illustrate the adjusted relationship between protein intake and the subdistribution hazard of extubation, predicted cumulative incidence functions (CIFs) were generated using the Fine-Gray model. Hypothetical covariate profiles were created by fixing all covariates at their median levels and using the first quartile, median, and third quartile of protein intake in the first week of feeding. Predicted CIFs were generated up to 28 days, representing the cumulative probability of extubation by that time point. The analyses and data visualizations were done using R statistical software using the cmprsk package.[14]

To determine whether BUN influenced the relationship between protein intake and the number of VFDs, an exploratory causal mediation analysis was performed using nonparametric bootstrap method (500 simulations)[15,16]. The primary independent variable was mean protein intake in g/kg/day, as calculated previously. The mediator was maximum BUN during the second week of ICU admission, and the outcome of interest was VFDs. The mediator model examined the association between protein intake and peak BUN levels, which was modelled with linear regression. The outcome model assessed the effect of both protein intake and peak BUN levels on VFDs which was modelled similarly. Both the mediator and outcome models were adjusted for the previously mentioned covariates, with additional adjustment for admission BUN levels and maximum creatinine level in the same time period. The average causal mediation effect (ACME), representing the indirect effect of protein intake on VFDs explained by BUN, average direct effect (ADE) of BUN on VFDs, and the total proportion mediated by BUN were calculated based on these models. To assess the robustness of the mediation findings to potential unmeasured confounding, we conducted a mediation sensitivity analysis to evaluate how the ACME would change under the influence of unmeasured confounders. A sensitivity curve was generated, and the strength of confounding necessary to nullify the mediation effect was quantified.[17] Additionally, we reported the proportion of residual variance ($R^2$) that an unmeasured confounder would need to explain in both models to eliminate the mediation effect.

The subgroup sensitivity analysis was performed with similar methods as mentioned above. Baseline characteristics of patients receiving greater than 8 kcal/kg/day were compared with those receiving less than 8 kcal/kg/day using Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test or Fisher's exact test for categorical variables. An alpha of 0.05 was used for statistical significance for all statistical tests.

## Results

### *Participants and Cohort Characteristics*

The final cohort comprised 329 subjects. The cohort had a median age of 46 [30-59] years. There were 256 male (78%) male and 242 (74%) subjects of White race (Table 1). The median ISS was 34 [26-43]. Median BMI was 26.6 mg/kg$^2$ [23.5-30.2]. Median days on the ventilator in the first 28-day period was 14 [0, 20]. Forty subjects died within 28 days from ICU admission (12.1%). The median average protein intake in the first week was 1.6 [1.0-2.0] g/kg/day. The median average caloric intake was 12 [8.0-17.0] kcal/kg/day.

### *Subdistribution Hazard of Extubation and Secondary Outcomes*

In competing risks analysis, 1 g/kg/day higher mean protein intake during the first week of feeding was associated with a 34% lower subdistribution hazard of extubation (SHR 0.66, 95% CI: 0.53 to 0.81, $p<0.001$), accounting for death and adjusting for covariates (Table 2). Hypothetical patient profiles receiving 1.0 g/kg/day, 1.5 g/kg/day, and 2.0 g/kg/day were compared in the predicted cumulative incidence function graphs (Figure 1). The 1.0 g/kg/day group demonstrated the highest probability of extubation, followed by the 1.5 g/kg/day, and the 2.0 g/kg/day group had the lowest probability. The predicted cumulative incidence of extubation was 76.4% for 1 g/kg/day, 70.2% for 1.5 g/kg/day, and 63.7% for 2 g/kg/day at ICU day 28.

In terms of secondary outcomes, aspiration occurred in 19 (5.8%) patients. There were 96 (29%) patients who developed VAP and 24 (7.3%) who developed ARDS during the study period. After adjustment, there was no significant association between mean protein intake and the development of these secondary respiratory outcomes (Supplementary Table 1).

### *Causal Mediation Analysis*

In the mediator model, each 1g/kg/day increase in protein was associated with a 5.06 mg/dL rise in BUN after covariate adjustment (95% CI, 3.2 to 6.9; $p<0.001$, Table 3). In the outcome model, each 1 mg/dL increase in BUN was associated with a –0.17-day change in VFDs ($\beta=-0.17$, 95% CI: –0.24 to –0.10; $p<0.001$), and each 1 g/kg increase in protein intake was associated with a –2.68-day difference in VFDs ($\beta=-2.68$, 95% CI: –3.96 to –1.41; $p<0.001$), adjusting for the same covariates.

Causal mediation analysis using nonparametric bootstrap demonstrated that higher protein intake was associated with fewer VFDs. Each additional 1 g/kg/day of protein intake was associated with a reduction of 3.53 VFDs (total effect: –3.53 days; 95% CI: –4.81 to –2.30; $p < 0.001$, Table 3). Twenty-four percent of this effect was explained by increases in BUN (proportion mediated: 24%, 95% CI: 12.0% to 41.0%; $p < 0.001$). Elevated BUN mediated a reduction of 0.85 VFDs (ACME: –0.85 days; 95% CI: –1.29 to –0.46; $p < 0.001$), while the remaining reduction of the total effect of 2.68 VFDs was directly related to protein intake itself, independent of BUN (ADE: –2.68 days; 95% CI: –4.01 to –1.42; $p < 0.001$).

Mediation sensitivity analysis showed that the ACME of BUN was not highly robust to unmeasured confounding, indicating a modest degree of unmeasured confounding on both the mediator and the outcome could negate the observed indirect effect. An unmeasured confounder explaining approximately 4% ($R^2 = 0.04$) of the combined residual variance in both the mediator and outcome models would be sufficient to nullify the ACME.

### *Sensitivity Analyses*

A total of 90 patients who received less than 8 kcal/kg/day of nutrition during the first week of ICU admission were excluded, leaving 239 patients for sensitivity analysis. When compared with patients who received greater than 8 kcal/kg/day, differences were noted in the abbreviated injury severity scores (Supplemental Table 1). Fewer patients receiving less than 8 kcal/kg/day had severe head (39% vs 63%) and neck injuries (8.9% vs. 21%). However, more of these patients had severe chest (84% vs 70%), abdomen (51% vs 21%), upper extremity (10% vs 3.3%, $p = 0.02$), and lower extremity injuries (62% vs. 41%). Median ventilator days was higher in the group who received greater than 8 kcal/kg/day (13 [8,21] vs. 10 [6,18], $p = 0.03$), and 28-

day mortality was similar between the groups at 12% ($p > 0.9$). Median 28-day VFDs were 13 [0,19] in the ≥8 kcal/kg/day group versus 17 [0, 22] in the <8 kcal/kg/day group ($p=0.06$).

After accounting for competing risks and adjusting for covariates, each 1 g/kg/day increase in protein intake was associated with a 35% decreased hazard of extubation (SHR 0.65, 95% CI, 0.49 to 0.84; $p =0.001$). APACHE II score was also inversely associated with extubation (SHR 0.97, 95% CI, 0.95 to 0.99; $p = 0.03$). Secondary outcomes were not significantly associated with protein intake in this subgroup. Causal mediation analysis in this subgroup found each additional 1g/kg/day of protein intake to be associated with a reduction of 3.53 days in VFDs (total effect: –3.53 days; 95% CI: –1.27 to –0.17; $p < 0.001$). About 19% of this effect was explained by BUN (proportion mediated: 19%, 95% CI: 5.3% to 45.0%; $p < 0.001$). Elevated BUN mediated a reduction of 0.67 VFDs (ACME: –0.67, 95% CI: –1.22 to –0.21; $p < 0.001$) of the total effect, with remaining 2.86 reduction in VFDs being attributable to protein, independent of BUN (ADE: –2.8, 95% CI: –4.26 to –1.21; $p < 0.001$). Mediation sensitivity showed that an unmeasured confounder contributing 9% ($R^2 = 0.09$) of residual variance could nullify the mediation effect of BUN in this subgroup.

## Discussion

This study is a secondary analysis of a prior randomized trial and examined the relationship between early protein intake and clinical outcomes in critically ill trauma patients, a group underrepresented in nutritional research. In our analysis, we used a standardized definition of ventilator-free days (VFDs) at 28 days and applied competing risk regression to account for the mutually exclusive outcomes of extubation and death. We observed that higher protein intake during the first week of enteral feeding was associated with a lower hazard of successful extubation, after accounting for confounders and accounting for the competing risk of death. Secondary outcomes of ARDS, VAP, and aspiration were not found to be associated with protein intake. The lack of association with secondary outcomes suggests that protein does not significantly impact the incidence of these other respiratory complications within the scope of our analysis. VFDs is a composite outcome integrating death and not unexpectedly, factors influencing successful extubation and overall respiratory recovery involve more complex physiological pathways beyond the incidence of these individual complications. Furthermore, the mediation analysis revealed that higher protein intake was associated with fewer VFDs and that blood urea nitrogen (BUN) partially mediated the relationship between total protein intake and VFDs. This provides some insight into how protein administration might influence outcomes in critically ill trauma patients.

While nutrition may generally be thought to support recovery and facilitate earlier ventilator weaning, we did not observe that effect. The observed inverse relationship between protein intake and VFDs contrasts with the 2016 ASPEN recommendations that critically ill surgical and trauma patients  might benefit from higher protein intake above 2.0 g/kg/day.[5] Our findings are also consistent with existing literature suggesting dose-dependent harm related to protein strategies during the early acute phase, potentially due to enhanced metabolic stress or renal impairment.[7] Prior review of nutrition trials suggest a U-shaped relationship of protein intake with mortality, with findings recommending avoiding protein intake below 0.9 g/kg/day or above 1.6 g/kg/day in critically ill patients due to higher risks of mortality.[6] We tested this idea of a curvilinear relationship between protein intake and VFDs, which includes death in its definition, however the nonlinear relationship was not supported based on our model comparisons. As such, we are unable to confirm a "turning point" value of protein intake that is associated with less adverse outcomes.  This highlights a need for a formal meta-analysis of prior studies that statistically supports such a relationship and potentially identifies an ideal "mid-range" of protein intake.

The role of elevated BUN as a mediating variable in the association between protein intake and decreased VFDs provides further insight into potential mechanisms of BUN's studied effect on clinical outcomes. Prior research has identified elevated BUN as a prognostic marker for adverse outcomes in critically ill patients, suggesting its utility in identifying metabolic disturbances associated with critical illness.[7,19] Our study extends these findings by highlighting BUN as a potential physiological mediator independent of creatinine. Elevated BUN levels can reflect increased protein metabolism and impaired renal function, conditions which are frequently encountered in critically ill patients. Additionally, it may indicate protein being redirected toward acute-phase response pathways or being metabolized as an alternative energy source due to heightened metabolic stress and impaired nutrient utilization during acute critical illness.  Conversely, elevated BUN itself may directly contribute to harm, possibly through increased nitrogenous waste toxicity, exacerbating renal stress and subsequently impairing respiratory recovery. While our mediation analysis supports BUN's involvement in this pathway, our subsequent sensitivity analysis showed that even minor unmeasured confounding could nullify this association. This emphasizes the complexity and multifactorial nature of ICU outcomes. Future research should explore these distinct mechanisms to clarify whether elevated BUN primarily serves as a marker of underlying metabolic dysfunction and/or actively contributes to clinical deterioration.

The results of our sensitivity analysis by caloric intake groups were consistent with what we observed in the primary competing risk analysis, with a similar magnitude of effect. It is also important to note that patients who received less than 8 kcal/kg/day in the first week of feeding had a higher incidence of severe head, neck, chest, abdomen and extremity injuries. While overall initial APACHE scores and in-hospital mortality did not differ, these patients were likely more subject to multiple procedures decreasing the opportunities to reach nutrition goals. Patients receiving at least 8 kcal/kg/day had more time on the ventilator indicated by higher median ventilator duration and thus were more likely to accumulate more nutrition exposure. Although we adjusted for baseline covariates, residual confounding is likely—particularly secondary to time-varying factors such as evolving organ dysfunction, vasopressor requirements, or episodes of sepsis. Moreover, both calorie strata were well below standard guideline targets (25–30 kcal/kg/day); thus, the comparison may primarily distinguish patients too unstable to tolerate feeding from those who stabilized sufficiently to receive modest nutritional doses, rather than reflecting a true biological effect of nutrition on respiratory recovery. Despite differences in injury severity and clinical complexity, caloric intake did not modify the relationship between protein intake and the likelihood of extubation, indicating that the observed protein–extubation association is robust across caloric intake levels in this cohort.

## Limitations

This study has several limitations that should be acknowledged. Firstly, it is a secondary analysis of a single-center randomized trial, and despite statistical adjustments, residual confounding cannot be entirely excluded. Additionally, protein intake varied significantly among patients, and although this variation allowed examination across a broad intake spectrum, it may reflect clinical practice variability that could confound outcome assessments. The sensitivity of our mediation analysis to unmeasured confounding also warrants caution in interpreting BUN's mediating role in the relationship between protein and outcomes.

Despite these limitations, our results highlight critical considerations for clinical practice and future guidelines for nutrition in the critically injured trauma population. Specifically, our findings suggest caution in additional protein supplementation early in the ICU stay of these patients. The unique challenge of achieving protein targets in severely injured trauma patients underscores the relevance of our findings in this study. Further investigation into the biological mechanisms of the interplay between protein, renal impairment and physical stress from severe injury could refine nutritional recommendations tailored explicitly for trauma patients.

## Conclusion

In conclusion, our study suggests that higher amounts of enteral protein during the first 7 days following injury is harmful in critically ill trauma patients. Higher protein intake in the acute phase was associated with a lower probability of extubation, partly mediated by elevated BUN levels. These findings challenge current nutritional guidelines advocating for higher protein provision in trauma patients. Future trials should focus on clarifying optimal protein dosing and examining underlying biological mechanisms.

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Table 1. Characteristics of Study Cohort of Trauma Patients

| | **N = 329[1]** |
|---|---|
| **Age (years)** | 46 [30, 59] |
| **Sex** | |
| Female | 73 (22%) |
| Male | 256 (78%) |
| **Race/Ethnicity** | |
| Asian | 13 (4.0%) |
| Black | 23 (7.0%) |
| Hispanic | 34 (10%) |
| Native American | 10 (3.0%) |
| Unknown | 7 (2.1%) |
| White | 242 (74%) |
| **Body Mass Index (kg/m²)** | 26.6 [23.5, 30.2] |
| **NUTRIC Score** | 5 [4, 6] |
| **Injury Severity Score** | 34 [26, 43] |
| **Severe Abbreviated Injury Severity Scores[2]** | |
| **Head** | 185 (56%) |
| **Face** | 29 (8.8%) |
| **Neck** | 59 (18%) |
| **Chest** | 243 (74%) |
| **Abdomen** | 96 (29%) |
| **Spine** | 78 (24%) |
| **Upper Extremity** | 17 (5.2%) |
| **Lower Extremity** | 154 (47%) |
| | |
| **APACHE II Score** | 27 [23, 32] |
| **28-Day ICU Mortality** | 46 (14%) |
| **Total Ventilator Days** | 13 [8, 20] |
| **Ventilator-Free Days (28-day)** | 14 [0, 20] |
| **28-day ICU Mortality** | 40 (12%) |
| **Mean Protein Intake over 7 days (g/kg/day)** | 1.6 [1.0-2.0] |
| **Mean Caloric Intake over 7 days (kcal/kg/day)** | 12 [8, 17] |
| | |
| **Acute Respiratory Distress Syndrome** | 24 (7.3%) |
| **Ventilator-Associated Pneumonia** | 96 (29%) |
| **Aspiration** | 19 (5.8%) |

[1] Median [25th, 75th %iles]; n (%)

[2] Defined as Abbreviated Injury Severity Score ≥ 3

Table 2. Association of mean protein intake in the first 7 days (g/kg/day) with outcomes in 329 trauma patients in a competing risks framework

| | **SHR[1]** | **95% CI** | **p-value** |
|---|---|---|---|
| Protein intake, per g/kg/day | 0.66 | 0.53-0.81 | **<0.001** |
| Age | 0.99 | 0.99-1.001 | 0.09 |
| Injury Severity Score = 10-24 | 1.37 | 0.55-3.38 | 0.50 |
| Injury Severity Score ≥ 25 | 1.23 | 0.51-2.98 | 0.64 |
| APACHE II Score | 0.97 | 0.95-0.98 | **0.001** |

[1] Subdistribution Hazard Ratio aka probability (hazard of extubation) given VFDs >1 and ≤28 days if successfully extubated and VFDs=0 for death before 28 days or intubation ≥28 days

[2] Defined as ≥48 hours without reintubation in a 28-day survivor

Figure 1. Predicted cumulative incidence functions of extubation by protein intake over 7 days based on subdistribution hazard model

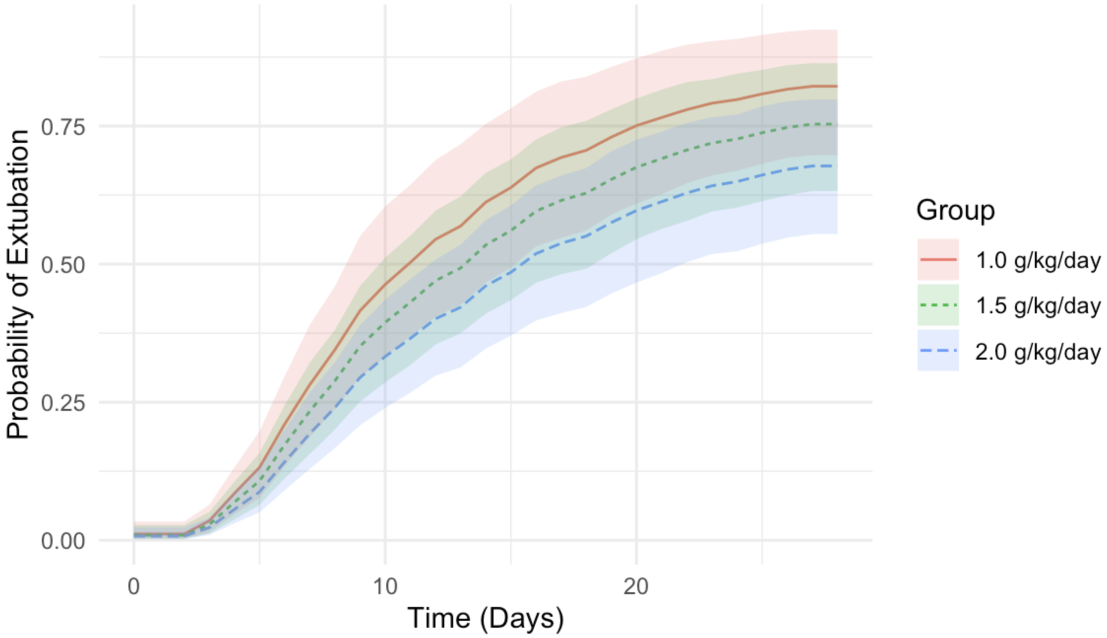

Table 3. Causal Mediation Analysis of BUN Effect on Protein Intake Relationship in g/kg/day with Ventilator-Free Days

| | **Estimate** | **95% CI** | **p-value** |
|---|---|---|---|
| Mediator Model[1] | β= 5.06 | 3.20, 6.92 | <0.001 |
| Outcome Model[2] | β= –2.68 | -3.96, -1.41 | <0.001 |
| Average Causal Mediation Effect (ACME) | -0.85 | -1.29-, -0.46 | **<0.001** |
| Average Direct Effect (ADE) | -2.68 | -4.01, -1.42 | **<0.001** |
| Total Effect (sum of ACME and ADE) | -3.53 | -4.81, -2.30 | **<0.001** |
| Proportion Mediated | 0.24 | 0.12, 0.41 | **<0.001** |

[1] Predictor: Mean protein intake (g/kg/day): Outcome: BUN

[2] Predictors: Mean protein intake (g/kg/day), BUN; Outcome: VFDs

Supplementary Table 1. Adjusted Association of Protein Intake (per g/kg/day) with Secondary Outcomes, from Logistic Regression Models

| Outcome[1] | **Estimate** | **95% CI** | **p-value** |
|---|---|---|---|
| Acute Respiratory Distress Syndrome | 0.52 | -0.17, 1.24 | 0.14 |
| Ventilator-Associated Pneumonia | -0.11 | -0.54, 0.32 | 0.62 |
| Aspiration | 0.70 | -0.08, 1.54 | 0.09 |

[1] adjusted for age, APACHE score, and ISS

Supplementary Table 2. Patient Characteristics by Calorie Intake Groups

| | **Calorie Groups** | | |
|---|---|---|---|
| | **<8 kcal/kg/day**, N = 90[1] | **≥8 kcal/kg/day**, N = 239[1] | **p-value**[2] |
| **Age (years)** | 48 [31, 59] | 45 [30, 59] | 0.7 |
| **Sex** | | | 0.6 |
| Female | 18 (20%) | 55 (23%) | |
| Male | 72 (80%) | 184 (77%) | |
| **Race/Ethnicity** | | | 0.4 |
| Asian | 4 (4.4%) | 9 (3.8%) | |
| Black | 8 (8.9%) | 15 (6.3%) | |
| Hispanic | 8 (8.9%) | 26 (11%) | |
| Native American | 1 (1.1%) | 9 (3.8%) | |
| Unknown | 0 (0%) | 7 (2.9%) | |
| White | 69 (77%) | 173 (72%) | |
| **Body Mass Index (kg/m²)** | 27.8 [24.8, 30.1] | 26.2 [22.9, 30.3] | **0.050** |
| **NUTRIC Score** | 5 [4, 5] | 5 [4, 6] | 0.6 |
| **Injury Severity Score** | 34 [26, 45] | 34 [26, 43] | 0.5 |
| **Severe Abbreviated Injury Severity Scores**[3] | | | |
| **Head** | 35 (39%) | 150 (63%) | **<0.001** |
| **Face** | 7 (7.8%) | 22 (9.2%) | 0.7 |
| **Neck** | 8 (8.9%) | 51 (21%) | **0.01** |
| **Chest** | 76 (84%) | 167 (70%) | **0.01** |
| **Abdomen** | 46 (51%) | 50 (21%) | **<0.001** |
| **Spine** | 20 (22%) | 58 (24%) | 0.69 |
| **Upper Extremity** | 9 (10%) | 8 (3.3%) | **0.02** |
| **Lower Extremity** | 56 (62%) | 98 (41%) | **<0.001** |
| | | | |
| **APACHE II Score** | 28 [22, 33] | 27 [23, 32] | >0.9 |
| **28-Day ICU Mortality** | 11 (12%) | 29 (12%) | >0.9 |
| **Total Ventilator Days** | 10 [6, 18] | 13 [8, 21] | **0.03** |
| **Ventilator-Free Days (28-day)** | 17 [0, 22] | 13 [0, 19] | 0.06 |
| **Mean Protein Intake over 7 days (g/kg/day)** | 0.9 [0.4, 1.4] | 1.7 [1.3, 2.1] | **<0.001** |
| **Average Caloric Intake (kcal/kg/day)** | 4 [2, 6] | 15 [11, 18] | **<0.001** |
| | | | |
| **Acute Respiratory Distress Syndrome** | 3 (3.3%) | 21 (8.8%) | 0.09 |

| | | | |
|---|---|---|---|
| **Ventilator-Associated Pneumonia** | 17 (19%) | 79 (33%) | **0.01** |
| **Aspiration** | 3 (3.3%) | 16 (6.7%) | 0.20 |

[1] Median [25th, 75th %iles]; n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
[3] Defined as Abbreviated Injury Severity Score ≥ 3

Supplementary Table 3. Association of total enteral protein intake (g/kg/day) in the first week of feeding, with outcomes in trauma patients receiving >8kcal/kg/day

| | **SHR** | **95% CI** | **p-value** |
|---|---|---|---|
| Protein intake, per g/kg/day | 0.65 | 0.49, 0.84 | **0.001** |
| Age (per year) | 0.99 | 0.98, 1.002 | 0.12 |
| ISS=10-24 | 1.36 | 0.53, 3.48 | 0.50 |
| ISS ≥25 | 1.20 | 0.49, 2.99 | 0.64 |
| APACHE II Score | 0.97 | 0.95, 0.98 | **0.03** |

Supplementary Material: Methods

# Supplemental enteral protein in critically ill trauma and surgical patients: A randomized clinical trial

## *Study design and setting*

From November 15, 2016, to November 26, 2021, we conducted a clinical trial in which critically ill trauma and surgical patients were randomized to early enteral protein supplementation or to standard enteral nutritional support (ClinicalTrials.gov ID: NCT03170401). All subjects were enrolled at a single Level 1 trauma center. The intensivists providing care to eligible patients agreed that there was collective clinical equipoise regarding the treatment arms. The study protocol was approved by the institutional IRB (STUDY00007918) and we report our findings in accordance with the CONSORT 2010 guidelines.

## *Study subjects, randomization, and outcomes assessment*

Potential subjects included those admitted to the trauma and surgical intensive care service. Patients were screened and were considered for inclusion if they were receiving mechanical ventilation, expected to require ICU care for at least 7 days, deemed ready to start enteral nutritional support within 24 – 72 hours of admission, and had no contraindications to full enteral support. Patients were excluded if they had severe chronic liver disease, chronic kidney disease, metastatic cancer, or were expected to die due to the severity of their illness or injuries. Potential subjects were enrolled after they or their surrogate provided informed consent. We did not have

7-day per week coverage for subject enrollment. Therefore, patients who may have met inclusion criteria were not enrolled when study personnel were unavailable. Subjects were randomized to a treatment arm using sealed envelopes. The study dietitian was not blinded to treatment assignment but did not participate in outcome assessment. The lead investigator was not involved in randomization or in the assessment of outcomes. Co-investigators assessing adverse events were blinded to the treatment arm.

### *Description of treatments and general clinical care*

Once deemed ready to receive enteral nutrition, patients were prescribed a polymeric formula with 1 – 1.5 kcal/ml. Continuous infusion started at 20 ml/hour and the rate was advanced over 24 hours to a goal of 25 kcal/kg/day delivered by continuous infusion via an orogastric or nasogastric tube. Caloric and protein targets were determined using actual body weight for patients with BMI $\leq 30$ and adjusted body weight for those $> 30$. Replete (Nestle Health Science, USA. 1.0 kcal/ml, 62.4 g/l protein, 25% kcal from protein) was the primary enteral formula that we used in our ICU during the study period. Monitoring for intolerance was primarily by clinical examination and followed generally accepted guidelines.

The study dietitian calculated caloric and protein needs for each patient. Supplemental protein (Prosource; Medtrition, Lancaster, PA) was administered over 1 – 2 minutes via the nasal/oral feeding tube in 60 – 180 ml bolus infusions 2 – 4 times per day. The daily target amount of protein was administered as the supplement boluses and once the enteral formula infusion approached the target rate the amount of supplemental protein was reduced as follows: a. supplemental protein was reduced by 50% once the patient received 75% of targeted caloric intake over the previous day, b. once the patient reached the target caloric intake for 48 hours, the amount of supplemental protein was adjusted in order that the total protein prescribed equaled approximately 1 g/kg/day.