Invasive Mechanical Ventilation and Nutrition Intake in Association with Serious Outcomes among COVID-19 ICU Patients

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ABSTRACT

Background: Worse clinical outcomes have been reported among critically ill COVID-19 patients who are admitted to an inpatient intensive care unit (ICU), especially those who require invasive mechanical ventilation (IMV). Patients on IMV do not receive any food or medication by mouth, during which their energy and protein needs are dependent on enteral nutrition (EN) and propofol lipid emulsion delivery (and parenteral nutrition if needed). Underfeeding throughout the ICU stay has been reported, while overfeeding due to propofol delivery is also a concern, which were both reported to be harmful to critically ill patients. However, there are limited data on the nutrition intake of COVID-19 patients during IMV and the association with in-hospital mortality.

Objectives: In this study, we examined whether IMV is associated with higher mortality and longer ICU length of stay in critically ill ICU patients admitted with COVID-19. We calculated the energy and protein intake from EN and the lipid emulsion for propofol and also evaluated the associations with in-hospital mortality.

Methods: We conducted a hospital-based retrospective study, using chart review of electronic medical records among COVID-19 patients admitted to an ICU at Harborview Medical Center (HMC) in Seattle, Washington, between March 5, 2020, through October 31, 2020. Multivariable logistic regression models were used to assess the associations between IMV and in-hospital mortality. Among those who survived to hospital discharge, multivariable linear regression was used to estimate the associations between IMV and ICU length of stay. Among those who received IMV during their hospital stay, we used multivariable logistic regression to estimate the associations between the nutrition intake during IMV and in-hospital mortality.

Results: Ninety-five patients were included in the chart review. The mean age was 60.9 [standard deviation (SD): 16.1] years and 78.9% were men. About half (50.5%) received IMV during hospitalization; 33.7% died prior to hospital discharge. After adjustment for demographics, the odds of in-hospital mortality was 3.28 (95% CI: 1.12, 9.59) times higher among patients who received IMV than those who did not ($p = 0.03$). The association was slightly attenuated after further adjustment for comorbidities [adjusted odds ratio (aOR) = 3.01 (95% CI: 0.97, 9.39), $p = 0.06$], prior medication use [aOR = 3.04 (95% CI: 0.96, 9.58), $p = 0.06$], and Sequential Organ Failure Assessment (SOFA) score [aOR = 2.92 (95% CI: 0.84, 10.15), $p = 0.09$]. Among the sixty-three patients who survived to hospital discharge, we found that patients receiving IMV were in the ICU 19.4 days longer (95% CI: 11.6, 27.3), than those who did not receive IMV after adjustment for demographics, comorbidities, prior medication use, and SOFA score ($p < 0.001$). Among the forty-three patients who received IMV and EN support during IMV, the in-hospital mortality was 44.2%. The mean total energy intake during IMV from EN and propofol administration was 1,890 (SD: 416.2) kcal/d. On average, this met 93.4 (SD: 16.9) percent of the energy intake goal set by the HMC clinical nutritionists. The mean energy intake per ideal body weight (IBW) was 26.9 (SD: 5.2) kcal/kg/d and 20.5 (SD: 11.8) percent of total energy, on average, was from propofol administration. The mean overall protein intake was 82.9 (SD: 21.1) g/d meeting, on average, 66.9 (SD: 16.7) percent of the protein intake goal. The mean

protein intake per IBW was 1.2 (SD: 0.3) g/kg/d. We found no evidence that the amount of energy intake per IBW was associated with in-hospital mortality. However, for each 0.1 g/kg/d increase of protein, the odds of in-hospital mortality was 46 (95% CI: 13, 64) percent lower among the patients with higher protein intake after adjustment for demographics, comorbidities, SOFA score, and receipt of extracorporeal membrane oxygenation (ECMO) ($p = 0.01$). The association remained significant after further adjustment for total energy intake per IBW [aOR = 0.47 (95% CI: 0.23, 0.98), $p = 0.04$].

Conclusion: Our study found that receiving IMV was associated with higher in-hospital mortality after adjustment for demographics among COVID-19 patients admitted to an ICU. IMV was an independent predictor of longer ICU length of stay. Among patients who received IMV and EN during hospitalization, deficits were larger for protein intake than for energy during IMV. Higher protein intake during IMV was a protective factor for in-hospital mortality. More clinical attention should be placed on nutrition delivery during IMV, especially protein intake. Studies with a larger sample size, more rigorous study designs, using more accurately measured daily nutritional needs, and addressing the intra- and inter-individual nutrition variability are needed to further elucidate the impact of nutrition intake during IMV on clinical outcomes of COVID-19 patients.

Keywords: COVID-19, Critically ill patient, Invasive mechanical ventilation, Enteral nutrition, Propofol

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome from coronavirus SARS-CoV-2, has spread globally, and is continuously challenging the healthcare system. As of May 18, 2021, COVID-19 has affected approximately 164 million individuals worldwide, and 33 million in the United States (US), causing an estimated 3.4 million deaths globally and 0.6 million deaths nationally.[1] The total number of COVID-19-associated hospitalizations among the U.S. population is 178,504 according to the Centers for Disease Control and Prevention (CDC) surveillance data as of May 08, 2021.[2] Studies have reported that 20-40% of hospitalized COVID-19 patients were treated in hospital intensive care units (ICU)[3-5] with an estimated 25% receiving invasive mechanical ventilation (IMV).[5] Mortality of these patients is high; 30-63% requiring intensive care do not survive to hospital discharge.[3, 5-7] Mortality for those who required IMV has been reported to be 45-83%.[5, 7] These numbers raise concern about the prognosis among critically ill COVID-19 patients, especially those who require IMV.

Many characteristics of COVID-19 patients have been reported to be associated with worse clinical outcomes. It was reported that older age, male sex, Black race, presenting problems related to respiratory function and comorbidities such as obesity, diabetes, and hypertension were associated with increasing oxygenation requirements and higher risk of mechanical ventilation.[8-11] Demographics such as older age, and male sex, having more comorbidities, as well as requiring ICU and ventilation have been found to be associated with higher mortality.[5, 9, 11-16] The prior use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blocker (ARBs) has been controversial in terms of COVID-19 severity and outcomes, and the results from existing studies have been mixed.[17-20] Moreover, statin use was reported to be associated with improved 28-day mortality in patients hospitalized with COVID-19 infection.[21] However, far less attention has been directed toward nutrition intake during COVID-19 hospitalization.

IMV has been leveraged for critically ill COVID-19 patients under the rationale that it reduces mortality in patients experiencing acute hypoxemic respiratory failure, the most common complication of COVID-19 associated acute respiratory distress syndrome (ARDS).[22, 23] However, the intubation process involved during IMV prevents patients from oral food intake. Unlike non-invasive ventilation (NIV) which is delivered through an alternative interface, usually a face mask, a patient on IMV is connected to the ventilator with a hollow tube (artificial airway) that goes through the mouth and down into the main airway or trachea. Thus, patients on IMV do not receive any food or medication by mouth. Instead of oral food, enteral nutrition (EN), also known as tube feeding, is provided to meet patients' macro- and micro-nutrients needs during IMV through a feeding tube.

It is reported that both underfeeding and overfeeding is harmful to critically ill patients.[24] A growing body of evidence indicates that persistent underfeeding throughout the ICU stay, particularly protein underfeeding, may significantly contribute to long-term mortality and quality of life (QoL) impairment months later.[25] The combination of stress and undernutrition that may occur in the ICUs is associated with negative energy balance, which leads to lean body mass loss. Catabolism of lean body mass has been associated with a worsening of clinical outcomes, increased length of hospital stay, longer recovery and higher healthcare costs.[26] On the other hand, overfeeding is related to complications such as hyperglycemia, hypercapnia, hypertriglyceridemia, and hepatic steatosis.

In IMV patients, the goal to avoid overfeeding may sometimes, in practice, lead to underfeeding. The

reason is that propofol (2,6-diisopropylphenol), a sedative-hypnotic agent widely used for both induction and maintenance of sedation in critical care units and is often concurrently administered among intubated COVID-19 ICU patients, could influence the EN delivery. Because propofol is poorly soluble in water, it is formulated in a 10% soybean oil-based lipid emulsion as its carrier. Thus, propofol provides a caloric content of 1.1 kcal/ml and contributes to the overall energy delivery. To prevent overfeeding, the EN delivery is adjusted in practice according to the administered propofol dose,[27-29] which may cause underfeeding especially in protein deficits. Researchers in the Longitudinal Energy Expenditure and Metabolic Effects in Patients With COVID-19 (LEEP-COVID) Study reported progressive hypermetabolism in measured resting energy expenditure (mREE) over the course of the ICU stay among mechanically ventilated COVID-19 patients.[30] However, the actual amount of energy and protein delivery during IMV, and the association with clinical outcomes among COVID-19 ICU patients, are still unclear.

In this study, we tested the hypothesis that IMV is associated with higher mortality and longer ICU length of stay in ICU patients admitted with COVID-19 (Aim 1). We calculated the energy and protein intake from EN and the lipid emulsion for propofol and also evaluated the associations with in-hospital mortality. We hypothesized that higher nutrition intake during IMV is associated with lower mortality (Aim 2).

The results of this study will contribute to the literature on survival and ICU length of stay among COVID-19 patients receiving IMV, the actual nutrition intake, and whether nutrition intake during IMV plays a role in in-hospital mortality. The results will assist clinical practice improvement from a nutritional perspective.

Methods

Study Design

We conducted a hospital-based, retrospective study, using chart review of electronic medical records (EMR) to collect data on COVID-19 ICU patients at Harborview Medical Center (HMC) in Seattle, WA. In aim 1, the outcomes of interest are in-hospital mortality and ICU length of stay. The exposure is receiving IMV during the hospital stay. In aim 2, the outcome is in-hospital mortality. The exposures are energy and protein intake during IMV. Covariates collected for inclusion in analyses were demographic factors, comorbidities, medication use prior to hospital admission, severity of illness, and having ever received extracorporeal membrane oxygenation (ECMO) support during hospitalization. These are described in greater detail under Data Collection.

Study Setting

This study was conducted on all COVID-19 patients admitted to the ICU at HMC, a comprehensive healthcare facility and the only level 1 trauma and burn center in Seattle WA. HMC is owned by King County and managed under contract by the University of Washington (UW). HMC cares for a wide range of patients across the region from UW faculty and staff to the un- and under-insured. The well-established electronic medical record system at HMC, Online Record of Clinical Activity (ORCA), allows abstraction of patient information through electronic chart review.

Study Subjects

The population eligible for this study were adult patients ≥ 18 years old admitted to HMC between March 5, 2020 through October 31, 2020, with a COVID-19-related admission, no prior COVID-19-related inpatient encounter at HMC, COVID-19-tested positive before or during hospitalization, and admitted to the ICU during the hospitalization (aim 1). In the second part of this study (aim 2), subjects were restricted to COVID-19 ICU patients who received IMV and EN support during hospitalization. Study procedures were approved by the UW Division of Human Subjects Institutional Review Board (IRB).

Data Collection

Data, including patient demographics, selected comorbidities, clinical characteristics, propofol administration, and EN delivery, were manually extracted from the EMR. The nutritional components, including energy and protein, of each EN product were collected from nutrition facts labels. All data were entered onto data collection forms using EpiData version 3.1 and exported to RStudio (Version 4.0.4, Vienna, Austria) for further cleaning and analysis by a Protecting Patient Information (HIPAA) trained abstractor and analyst (Y.W.).

Outcomes

In aim 1, evaluation of invasive mechanical ventilation, the outcomes of interest were in-hospital death (binary indicator of 1/0) and ICU length of stay (days). The ICU admission, discharge date and time, accurate to minute, were used to calculate ICU length of stay. In aim 2, evaluation of nutritional intake, the outcome was in-hospital death.

Exposures

In aim1, the exposure was receipt of IMV (1/0) at any time during current inpatient encounter. It was defined as receiving IMV through the endotracheal tube during which the patients were not able to take oral food.

In aim 2, the exposures were daily energy intake per ideal body weight (IBW) (kcal/kg/d) and daily protein intake per IBW (g/kg/d) during IMV. The period of IMV started from intubation to extubation, discharge, or death. The IMV start and end date and time were recorded and used to calculate length on IMV ($LENGTH_{IMV}$). Nutritional intake during IMV was determined from propofol administration and EN delivery [excluding parenteral nutrition (PN) which is rare]. Total propofol administration volume (ml) during IMV was collected and used to calculate total energy intake from propofol administration as shown below:

$$E_{propofol}\ (kcal) = 1.1\ kcal/ml * total\ propofol\ administration\ (ml).$$

The total volume of each EN product delivered during IMV was recorded and used to calculate the total energy intake from EN (E_{EN}). The IBW was calculated using the Devine formula [31] differentiating obese and not obese patients. The calculation used for non-obese patients (BMI ≤ 30 kg/m^2) was:

$$IBW_{Male}\ (kg) = 50 + 2.3*(height\ inches - 60);\ IBW_{Female}\ (kg) = 45.5 + 2.3*(height\ inches - 60).$$

In obese patients (BMI > 30 kg/m^2), the adjusted IBW was calculated as the average of actual weight

on admission and the unadjusted IBW using the Devine formula:.

$$\text{Daily energy intake per IBW (kcal/kg/d)} = (E_{propofol} + E_{EN}) / (LENGTH_{IMV} \cdot IBW).$$

EN was the only source of protein intake during IMV. The total volume of each EN product delivered during IMV and the nutrition components information were used to calculate the total nutrition intake during IMV ($PROTEIN_{EN}$):

$$\text{Daily protein intake per IBW (g/kg/d)} = PROTEIN_{EN} / (LENGTH_{IMV} \cdot IBW).$$

Covariates

Demographic factors abstracted from the EMR included patient age on ICU admission (in years), sex (male or female) and race/ethnicity. Race/ethnicity was classified as Non-Hispanic White, Hispanic, Non-Hispanic Black, Non-Hispanic Asian, Non-Hispanic Others and unknown in aim 1. In aim 2, race/ethnicity was re-categorized as Non-Hispanic White, Others, and Unknown, due to small counts in most categories to allow for better fit in regression models. Comorbidities included body mass index (BMI) on ICU admission, and past medical history of type 2 diabetes (T2D), hypertension (HTN), cardiovascular disease (CVD), and chronic obstructive pulmonary disease (COPD). BMI was calculated as a person's weight in kilograms divided by the square of height in meters. It was categorized as underweight (less than 18.5), normal (18.5 to < 25), overweight (25.0 to <30), and obese (30.0 or higher) according to the cut points recommended by the Centers for Disease Control and Prevention (CDC).[32] Medication use prior to hospital admission included ACEIs, ARBs, and Statins. Severity of illness was evaluated by Sequential Organ Failure Assessment (SOFA) score on ICU admission.[33] Receipt of ECMO during hospital stay was included in aim 2 but not aim 1, because only patients who received IMV had the opportunity to receive ECMO. The selection of covariates was based on reports in the literature which suggest a potential association with COVID-19 clinical outcomes. In order to maximize the sample of patients included in each model, we categorized missing data for some covariates (i.e., race/ethnicity and BMI) as "unknown". As patients with missing race/ethnicity and BMI were often too sick to report their information, it may be reasonable to assume that those grouped together as unknown had certain similarities regarding severity of illness.

Data Analysis

Multivariable logistic regression was used to assess the associations between IMV and in-hospital mortality in unadjusted models and after adjustment for covariates. Among those who survived to hospital discharge, multivariable linear regression models were used to estimate the associations between IMV and ICU length of stay. Among those who received IMV during hospital stay, we used multivariable logistic regression to estimate the associations between nutritional intake during IMV and in-hospital mortality unadjusted and after adjustment for covariates. The unadjusted models included only the exposure to evaluate the crude association between each variable and each outcome.

We used a hierarchical adjustment approach for adding potential confounders into models for each clinical outcome. Specifically, demographics, comorbidities, prior medication use, and SOFA score were

added to the previous model in aim 1. The receipt of ECMO was also added in the final model in aim 2. COPD and prior medication use were not included in aim 2 due to low numbers of use.

Continuous variables were expressed as mean [standard deviation (SD)]. Categorical variables were presented as counts (percentage). Huber-White robust standard errors were used to construct the 95% confidence intervals (CIs) and to calculate the p-values. A two-sided p-value of less than 0.05 was considered statistically significant for these analyses. Data management and statistical analyses were conducted in R (RStudio version 4.0.4) in RStudio.

Results

Aim 1: Associations between IMV, In-Hospital Mortality and ICU Length of Stay

A total of 95 patients with a COVID-19-related admission were admitted to the ICU at HMC between March 5, 2020, and October 31, 2020, and were included in this study. Patients ranged in age from 29 to 97 years with a mean age of 60.9 (SD: 16.1) years; seventy-five (78.9%) were men (**Table 1**). Thirty-two (33.7%) died prior to hospital discharge. Overall, forty-eight (50.5%) received IMV during hospitalization. Compared to patients who did not receive IMV, IMV patients tended to be younger [mean age 57.9 (14.0) vs. 64.0 (17.6) yrs], more likely to be male [forty-two (87.5%) vs. thirty-three (70.2%)], have a higher BMI [30.8 (6.2) vs. 27.4 (6.3) kg/m^2], classified with obesity [twenty-six (54.2%) vs. eleven (23.4%)], have type 2 diabetes [twenty (41.7%) vs. fifteen (31.9%)], have a higher SOFA score [4.98 (4.31) vs. 2.43 (2.80)], and more likely to die in-hospital [twenty (41.7%) vs. twelve (25.5%)). Notably, eighteen (38.3%) of non-IMV patients requested "do-not-intubate" (DNI) order.

By fitting a simple logistic regression model, we found that the odds of in-hospital mortality was 2.08 (95% CI: 0.87, 4.98) times higher among patients who received IMV during their hospital stay than those who did not (**Table 2**). After adjustment for demographics, the odds of in-hospital mortality were 3.28 (95% CI: 1.12, 9.59) times higher among patients who received IMV than those who did not ($p = 0.03$). The association was attenuated after further adjustment for comorbidities [adjusted odds ratio (aOR) = 3.01 (95% CI: 0.97, 9.39), $p = 0.06$], prior medication use [aOR = 3.04 (95% CI: 0.96, 9.58), $p = 0.06$], and SOFA score [aOR = 2.92 (95% CI: 0.84, 10.15), $p = 0.09$]. We found older age to be an independent risk factor of higher in-hospital mortality, with each year associated with 7% (95% CI: 2%, 13%) higher in-hospital mortality after adjustment for IMV, other demographics, comorbidities, prior medication use, and SOFA score ($p = 0.009$).

Among the 63 patients who survived to hospital discharge, we found that receipt of IMV was an independent predictor of longer ICU length of stay compared to those that were not intubated (**Table 3**). Patients receiving IMV were in the ICU 19.4 days longer (95% CI: 11.6, 27.3), than those who did not after adjustment for demographics, comorbidities, prior medication use, and SOFA score ($p < 0.001$). In sensitivity analyses, in which we excluded two patients with extremely long ICU lengths of stay 3 or more SDs from the mean (**Figure 1**), the association between receipt of IMV and longer ICU length of stay remained significant (p=0.001) (**Appendix** Table 1).

Aim 2: Associations between Nutritional Intake During IMV and In-Hospital Mortality among Patients Receiving IMV

There were 48 patients who received IMV during hospitalization. Five who had too short of a stay on

IMV (< 24h) to receive any EN support were excluded from the nutrition-related analyses in aim 2. Among the 43 patients who received IMV and EN support during IMV, the total number of in-hospital deaths was nineteen (44.2%) (**Table 4**). Compared to patients who survived to hospital discharge, patients who died tended to be older [61.3 (11.2) vs. 54.0 (16.1) yrs], more likely to be non-White race/ethnicity [fourteen (73.7%) vs. fifteen (62.5%)], have type 2 diabetes [eleven (57.9%) vs. six (25%)], and to have previous used statins [eight (42.1%) vs. five (20.8%)].

Overall, the mean total energy intake during IMV from EN and propofol administration was 1,890 (SD: 416.2) kcal/d. This met 93.4 (16.9) percent of the energy intake goal set by the clinical nutritionists (**Table 4**). The mean energy intake per IBW was 26.9 (5.2) kcal/kg/d and 20.5 (11.8) percent of total energy was from propofol administration. The mean overall protein intake was 82.9 (21.1) g/d meeting 66.9 (16.7) percent of the protein intake goal set by the clinical nutritionists. The mean protein intake per IBW was 1.2 (0.3) g/kg/d.

In logistic regression models adjusted for demographics, comorbidities, SOFA score, and receipt of ECMO, there were no associations between the amount of energy intake per IBW and in-hospital mortality (**Table 5**). However, an association between protein intake and in-hospital mortality was identified. We found that for each 0.1 g/kg/d increase of protein, the odds of in-hospital mortality were 46 (95% CI: 13, 64) percent lower among the patients with higher protein intake after adjustment for demographics, comorbidities, SOFA score, and receipt of ECMO ($p = 0.01$) (**Table 6**). The association between protein intake per IBW and in-hospital mortality remained significant after further adjustment for total energy intake per IBW [aOR = 0.47 (95% CI: 0.23, 0.98), $p = 0.04$] (**Table 7**). In addition, older age and type 2 diabetes were two independent risk factors for higher in-hospital mortality among the patients who received IMV. Specifically, each year of older age was associated with 17% (95% CI: 6%, 29%) higher in-hospital mortality after adjustment for energy and protein intake, other demographics, comorbidities, SOFA score, and receipt of ECMO ($p = 0.002$), while type 2 diabetes was associated with 8.43 (95% CI: 1.24, 57.19) times higher odds of in-hospital mortality after adjustment for the other covariates ($p = 0.03$).

In sensitivity analyses, we excluded 1 patient whose length on IMV was 115.7 days (> mean + 3*standard deviation) from the nutrition related analysis (**Figure 2**). The associations between nutrition intakes and in-hospital mortality did not vary substantially (**Appendix** Table 2, 3, and 4).

Discussion

In this hospital-based retrospective study among COVID-19 patients admitted to ICU over an 8-month period at HMC, we found that receiving IMV during hospitalization was associated with higher in-hospital mortality after adjustment for demographics. The associations between IMV and in-hospital mortality were slightly attenuated after further adjustment for comorbidities, prior medication use, and SOFA score. IMV was an independent predictor of longer ICU length of stay. Among patients who received IMV and EN during hospitalization, the deficit was larger for protein than for energy intake during IMV. Higher protein intake during IMV reduced the risk of in-hospital mortality after adjustment for demographics, comorbidities, SOFA score, and the reception of ECMO. The protective association remained after further adjustment for energy intake.

Our results are consistent with the increasing literature reporting worse outcomes among COVID-19 patients receiving IMV.[5, 10] Patients with more severe illness tended to receive IMV during

hospitalization and were more likely to have worse clinical outcomes. Although we attempted to adjust for severity of disease in patients requiring IMV by adjusting for the SOFA score on ICU admission, it is possible that the reason worse outcomes were observed was due to residual confounding. For example, there were certain measurements, such as low PaO_2/FiO_2 ratio, high serum D-dimer level, low lymphocyte count, and high creatinine,[11, 34, 35] associated with higher receipt of IMV and worse outcomes that were not collected which may have amplified the observed associations. It is also possible that some side effects of IMV may have led to differences in clinical outcomes. However, the detailed protocol on decision making in terms of ventilation during clinical practice is beyond the scope of the current study. The motivation of this study was to identify a practice that may improve survival among patients receive IMV from a nutritional perspective.

Delivery of optimal nutrition support is important but also challenging among IMV COVID-19 patients. Data on COVID-19 specific nutrition needs is limited. It has been recommended to use indirect calorimetry (IC) to estimate caloric goals.[24, 30, 36] Researchers in the LEEP-COVID Study assessed longitudinal resting energy expenditure (REE) via IC in 22 mechanically ventilated COVID-19 patients and reported progressive hypermetabolism and considerable variation in measured REE (mREE) over the course of the ICU stay.[30] Specifically, they reported the median mREEs were 20, 26, and 31 kcal/kg/d, respectively for the 1st, 2nd, and 3rd ICU week.[30] Another study performed 19 ICs in 6 COVID-19 patients during ventilation and reported a mean mREE of 21 kcal/kg/d.[37] The Harris-Benedict equation (HBE) is commonly used to predict the caloric needs in clinical practice due to its cost (none), ease of use, and availability.[38] However, the LEEP-COVID Study suggested that the HBE significantly under-predicted the caloric need post-1st ICU week among this population. For example, the mREE by IC was 1.5 times the REE predicted by HBE (pREE) during the 3rd ICU week.[30]

IC is not routinely performed in practice in most clinical settings. The clinical nutritionists at HMC use HBE times a stress factor of 1.2 - 1.4 to calculate the energy goal among COVID-19 patients. To prevent under- and overfeeding during IMV, alternative recommendations are made on EN delivery rates and dosages, according to different levels of propofol administration rate. In particular, as propofol dosage increases, the delivery rate and dosage of formulated EN products will decrease and specific EN protein supplement will be added. In this study, the mean actual energy intake including propofol administration was 1890 kcal/d or 26.9 kcal/kg/d, which is close to the mREE during the 2nd ICU week reported in the LEEP-COVID study. The energy intake met 93.4% of the energy goal set by the clinical nutritionists according to the nutrition notes.

The deficit was larger for protein than for energy intake during IMV in this study. Previous literature suggested that during critical illness, increased protein must be delivered to support protein synthesis and to maintain protein homeostasis in cells as protein catabolism exceeds anabolism.[39] The European Society for Clinical Nutrition and Metabolism (ESPEN) recommended a protein intake of 1.3 g/kg/d,[40] while some others recommended a higher intake of 1.5 – 2.0 g/kg/d during ventilation.[41]

In this study, the mean protein intake was 82.9 g/d or 1.2 g/kg/d and met 66.9% of the protein goal set by the clinical nutritionists. This is similar to a previous study which reported an protein delivery of 1.0 g/kg/d during acute phase (day 0-7) and 1.3 g/kg/d during late phase (> day 7) among mechanical ventilated COVID-19 patients.[42] The larger protein than energy deficit observed can be explained by propofol administration, which contributed an average of 20.5% of the total energy intake per person in this study.

Another study reported that non-nutritional energy (NNE), e.g., propofol, proportionately reduces feed protein prescription and contributed 19% of energy expenditure in 10% of critical ill patients.[43] As mentioned earlier, propofol administration during IMV will suppress the EN delivery. While formulated EN product delivery was decreased to prevent overfeeding, protein supplementation was not always considered. Studies have shown that providing high protein-containing EN formulas improved protein delivery without caloric overfeeding for critically ill patients, including those requiring high-dose propofol therapy.[43-46] Extrapolated from these studies, we suggest that protein supplements and/or high protein-containing EN formulas could be used when EN delivery is suppressed by NNE administration.

In this study, we did not find a significant association between energy intake during IMV and in-hospital mortality among COVID-19 patients, but a protective association between higher protein intake and in-hospital mortality was detected. Data on the associations between energy and protein intake and mortality in IMV COVID-19 patients is very limited. Mixed findings on the effect of energy intake were reported from different studies in general ICU settings. A randomized trial comparing permissive underfeeding (40-60% of the caloric target) to standard feeding (70-100% of the caloric target) in patients who received the same amount of protein, failed to find a benefit with higher energy intake.[47] Similarly, two randomized trials, comparing patients who received either low-volume or full-energy EN during the initial 6 days of mechanical ventilation, did not observe significant difference in ventilator-free days, 60-day mortality, or infectious complications, but found an association between initial low-volume EN and less gastrointestinal intolerance.[48, 49] On the other hand, a recently published observational study suggested that early caloric deficit is associated with a higher risk of death in invasive ventilated COVID-19 patients.[50] Observational studies among mechanically ventilated, critically ill patients, showed that providing more than two-thirds of prescribed calories was associated with reduced mortality,[24, 51] and suggested that providing > 85% of the caloric goal was associated with the best outcome,[51] but no additional benefit was found of feeding > 100% of the target.[51] The discrepancy from observational studies and randomized trials is possibly due to residual confounding in observational studies. For example, disease severity may lead to both poor caloric feeding and clinical outcome. Without fully controlling for disease severity in an observational study, we would expect to see an amplified association between energy intake and clinical outcome. Furthermore, REE appears highly variable among critically ill patients and in individual patients during various phases of illness.[52] The observed absence of association between energy intake during IMV and in-hospital mortality in the current study may be due to the potential coexisting of the negative effects from over- and/or under-feeding during early and/or late phases of the disease with mixed overall associations.

The observed protective association between higher protein intake during IMV and survival in our study aligns with previous studies in a non-COVID-19 setting.[24, 53-55] An observational study reported that overall low protein intake (<0.8 g/kg/d) was associated with the highest in-hospital, ICU, and 6-month mortality among mechanically ventilated ICU patients.[55] Another observational study showed reaching both protein and energy targets was associated with a decrease in 28-day mortality by 50%, whereas only reaching energy targets was not associated with a reduction in mortality among mechanically ventilated, critically ill patients.[53] In addition to the amount of protein intake, it was also reported that timing of protein intake may be relevant for optimizing ICU, in-hospital and long-term mortality outcomes.[52, 55, 56] An observational study reported that increasing protein intake from low on day 1-2 (<0.8 g/kg/d) to

intermediate on day 3-5 (0.8-1.2 g/kg/d) to high after day 5 (>1.2 g/kg/d) during mechanically ventilated in ICU conferred the best long-term outcome.[55]

Our study is one of the first studies to evaluate the associations between nutritional intake during IMV and COVID-19 in-hospital mortality and is the first study reporting higher protein intake during IMV to be a protective factor of in-hospital mortality. The results of this study will increase understanding of the associations between IMV and clinical outcomes among COVID-19 patients. Our study will also contribute to the limited data about the energy and protein intake during IMV, and the role of nutritional intake during IMV on in-hospital mortality. We hope that results will assist clinical practice improvement from a nutritional perspective.

There were several limitations in this study. First, this single center study only included patients admitted to HMC, so the generalizability of the study results may be limited due to potential differences in clinical practice in different settings. Second, the retrospective cross-sectional study design prevented us from drawing conclusions about causality. Third, the sample size was relatively small, especially in the nutrition-related analysis. However, all eligible patients from March 5, 2020 through October 31, 2020 had been included into this study. To improve fit of the models with small sample size, we excluded prior medication use from the covariates list in the nutrition related analysis. Fourth, we did not exclude patients who requested DNI from the analysis in aim 1 due to our small sample size. Thus, in our study population, patients who received IMV tended to be younger than those who did not as patients requested DNI were older. If older age is indeed an independent risk factor for higher in-hospital mortality as shown in this study and previous literature, [5, 9, 57, 58] we would expect to observe an even stronger association between the receipt of IMV and in-hospital mortality if the patients who requested DNI had not done so. Fifth, we did not extract the data on PN or dextrose containing fluids/medications. Although PN was rarely provided among our study population since EN was well tolerated, we might have misclassified the nutritional exposures which could affect study results. Furthermore, failure to consider the length of IMV and EN and dynamic nutritional needs is another limitation. It is possible that the length of IMV and EN is associated with differences in mortality. For example, comparing two patients who have the same amount of daily nutrition intake but differ in length receiving nutrition support, we might expect nutrition to contribute more to the outcome in the patient who receives longer nutrition support. In our setting which included both the deceased and survivors, patients who died could not continue to receive nutrition support. Therefore, adjusting for the length of IMV and EN is not reasonable. An alternative study design to take the length of IMV and EN into account would be survival analysis. However, we did not have the labor capacity to collect the nutrition intake for each day during IMV. Even had we been able to collect daily nutrition intake, we still had limited information about the individual dynamic nutritional needs during IMV, and it would not be possible to quantify the gap between nutrition needs and intake for each day (as the dynamic nutrition gap would be considered as a time-varying variable in survival analysis). Thus, a survival analysis study design would also be limited for these types of analyses.

Future research should focus on the development of tools to accurately measure the individualized dynamic energy and protein needs during IMV, and the application of these tools in guiding clinical nutritional support. Studies are also needed to address the effect of under- and/or overfeeding on clinical outcomes. Using more accurately measured daily nutrition needs and taking the variability of intra- and inter-individual nutrition needs into account are an alternate approach, preferably using a survival analysis

and/or randomized controlled trial (RCT) study design.

In conclusion, receiving IMV was associated with higher in-hospital mortality after adjustment for demographics among COVID-19 patients admitted to ICU. IMV was an independent predictor of longer ICU length of stay. Among patients who received IMV and EN during hospitalization, deficits were larger for protein intake than for energy during IMV. Higher protein intake during IMV was a protective factor for in-hospital mortality after adjustment for demographics, comorbidities, SOFA score, and the reception of ECMO. The protective association remained after further adjustment for energy intake. More clinical attention should be placed on nutrition delivery during IMV, especially protein intake. Studies with a larger sample size, using more accurately measured daily nutrition needs, addressing the intra- and inter-individual nutrition variability, and applying more rigorous study designs, are needed to further elucidate the impact of nutrition intake during IMV on clinical outcomes.

References

1. Dong, E., H. Du, and L. Gardner, *An interactive web-based dashboard to track COVID-19 in real time.* Lancet Infect Dis, 2020. **20**(5): p. 533-534.
2. *COVID-NET: COVID-19-Associated Hospitalization Surveillance Network, Centers for Disease Control and Prevention. WEBSITE. Accessed on May 18, 2021.*
3. Marcolino, M.S., et al., *Clinical characteristics and outcomes of patients hospitalized with COVID-19 in Brazil: results from the Brazilian COVID-19 Registry.* Int J Infect Dis, 2021.
4. Liu, Z., et al., *Different characteristics of critical COVID-19 and thinking of treatment strategies in non-elderly and elderly severe adult patients.* Int Immunopharmacol, 2021. **92**: p. 107343.
5. de Souza, F.S.H., et al., *On the analysis of mortality risk factors for hospitalized COVID-19 patients: A data-driven study using the major Brazilian database.* PLoS One, 2021. **16**(3): p. e0248580.
6. Auld, S.C., et al., *ICU and Ventilator Mortality Among Critically Ill Adults With Coronavirus Disease 2019.* Crit Care Med, 2020. **48**(9): p. e799-e804.
7. Lim, Z.J., et al., *Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. A Meta-analysis.* Am J Respir Crit Care Med, 2021. **203**(1): p. 54-66.
8. Simonnet, A., et al., *High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation.* Obesity (Silver Spring), 2020. **28**(7): p. 1195-1199.
9. Palaiodimos, L., et al., *Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York.* Metabolism, 2020. **108**: p. 154262.
10. Chang, R., et al., *COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis.* PLoS One, 2021. **16**(2): p. e0246318.
11. Ioannou, G.N., et al., *Risk Factors for Hospitalization, Mechanical Ventilation, or Death Among 10131 US Veterans With SARS-CoV-2 Infection.* JAMA Netw Open, 2020. **3**(9): p. e2022310.
12. Quan, D., et al., *Impact of Race and Socioeconomic Status on Outcomes in Patients Hospitalized with COVID-19.* J Gen Intern Med, 2021.
13. Zheng, Z., et al., *Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis.* J Infect, 2020. **81**(2): p. e16-e25.

14. Nikpouraghdam, M., et al., *Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study.* J Clin Virol, 2020. **127**: p. 104378.
15. Menter, T., et al., *Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction.* Histopathology, 2020. **77**(2): p. 198-209.
16. Bonanad, C., et al., *The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects.* J Am Med Dir Assoc, 2020. **21**(7): p. 915-918.
17. Banwait, R., et al., *Renin-Angiotensin-Aldosterone System Blockers Prior to Hospitalization and Their Association With Clinical Outcomes in Coronavirus Disease 2019 (COVID-19).* Cureus, 2021. **13**(2): p. e13429.
18. Zhou, F., et al., *Comparative Impacts of ACE (Angiotensin-Converting Enzyme) Inhibitors Versus Angiotensin II Receptor Blockers on the Risk of COVID-19 Mortality.* Hypertension, 2020. **76**(2): p. e15-e17.
19. Richardson, S., et al., *Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area.* JAMA, 2020. **323**(20): p. 2052-2059.
20. Mehta, N., et al., *Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19).* JAMA Cardiol, 2020. **5**(9): p. 1020-1026.
21. Memel, Z.N., et al., *Statins Are Associated with Improved 28-day Mortality in Patients Hospitalized with SARS-CoV-2 Infection.* medRxiv, 2021.
22. Tsikala Vafea, M., et al., *Mortality in mechanically ventilated patients with COVID-19: a systematic review.* Expert Rev Med Devices, 2021.
23. Alhazzani, W., et al., *Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19).* Intensive Care Med, 2020. **46**(5): p. 854-887.
24. Zusman, O., et al., *Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study.* Crit Care, 2016. **20**(1): p. 367.
25. Wischmeyer, P.E., *Nutrition Therapy in Sepsis.* Crit Care Clin, 2018. **34**(1): p. 107-125.
26. Thibault, R. and C. Pichard, *Nutrition and clinical outcome in intensive care patients.* Curr Opin Clin Nutr Metab Care, 2010. **13**(2): p. 177-83.
27. Chapple, L.S., et al., *Nutrition management for critically and acutely unwell hospitalised patients with coronavirus disease 2019 (COVID-19) in Australia and New Zealand.* Aust Crit Care, 2020. **33**(5): p. 399-406.
28. van Zanten, A.R.H., E. De Waele, and P.E. Wischmeyer, *Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases.* Crit Care, 2019. **23**(1): p. 368.
29. Buckley, C.T. and R.N. Dickerson, *Propofol: A Risk Factor for Caloric Overfeeding and Inadequate Protein Delivery.* Hosp Pharm, 2020. **55**(3): p. 151-152.
30. Whittle, J., et al., *Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19.* Crit Care, 2020. **24**(1): p. 581.
31. BJ, D., *Gentamicin Therapy.* Drug Intell Clin Pharm, 1974. **8**: p. 650 - 655.

32. *Defining Adult Overweight & Obesity*. [cited 2021 May 18]; Available from: https://www.cdc.gov/obesity/adult/defining.html.
33. Ferreira, F.L., et al., *Serial evaluation of the SOFA score to predict outcome in critically ill patients.* JAMA, 2001. **286**(14): p. 1754-8.
34. Turan, O., et al., *Clinical characteristics and outcomes of hospitalized COVID-19 patients with COPD.* Expert Rev Respir Med, 2021: p. 1-8.
35. Sarfaraz, S., et al., *Determinants of in-hospital mortality in COVID-19; a prospective cohort study from Pakistan.* PLoS One, 2021. **16**(5): p. e0251754.
36. Berger, M.M., *Nutrition and Micronutrient Therapy in Critical Illness Should Be Individualized.* JPEN J Parenter Enteral Nutr, 2020. **44**(8): p. 1380-1387.
37. De Waele, E., J. Demol, and J. Jonckheer, *Resting energy expenditure measured by indirect calorimetry: Ventilated Covid-19 patients are normometabolic.* Clin Nutr ESPEN, 2020. **40**: p. 631-2.
38. Bendavid, I., et al., *The centenary of the Harris-Benedict equations: How to assess energy requirements best? Recommendations from the ESPEN expert group.* Clin Nutr, 2021. **40**(3): p. 690-701.
39. Ochoa Gautier, J.B., et al., *How Much and What Type of Protein Should a Critically Ill Patient Receive?* Nutr Clin Pract, 2017. **32**(1_suppl): p. 6S-14S.
40. Barazzoni, R., et al., *ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection.* Clin Nutr, 2020. **39**(6): p. 1631-1638.
41. Stachowska, E., et al., *Nutritional Support in Coronavirus 2019 Disease.* Medicina (Kaunas), 2020. **56**(6).
42. Lakenman, P.L.M., et al., *Energy expenditure and feeding practices and tolerance during the acute and late phase of critically ill COVID-19 patients.* Clin Nutr ESPEN, 2021.
43. Taylor, S., et al., *Critical care: Meeting protein requirements without overfeeding energy.* Clin Nutr ESPEN, 2016. **11**: p. e55-e62.
44. Buckley, C.T., et al., *Improvement in Protein Delivery for Critically Ill Patients Requiring High-Dose Propofol Therapy and Enteral Nutrition.* Nutr Clin Pract, 2020.
45. Hopkins, B., et al., *Achieving Protein Targets in the ICU Using a Specialized High-Protein Enteral Formula: A Quality Improvement Project.* Nutr Clin Pract, 2020. **35**(2): p. 289-298.
46. ApSimon, M., et al., *Narrowing the Protein Deficit Gap in Critically Ill Patients Using a Very High-Protein Enteral Formula.* Nutr Clin Pract, 2020. **35**(3): p. 533-539.
47. Arabi, Y.M., et al., *Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults.* N Engl J Med, 2015. **372**(25): p. 2398-408.
48. National Heart, L., et al., *Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial.* JAMA, 2012. **307**(8): p. 795-803.
49. Rice, T.W., et al., *Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure.* Crit Care Med, 2011. **39**(5): p. 967-74.
50. Cereda, E., et al., *Early caloric deficit is associated with a higher risk of death in invasive ventilated COVID-19 patients.* Clin Nutr, 2021.

51. Heyland, D.K., N. Cahill, and A.G. Day, *Optimal amount of calories for critically ill patients: depends on how you slice the cake!* Crit Care Med, 2011. **39**(12): p. 2619-26.
52. Moonen, H., K.J.H. Beckers, and A.R.H. van Zanten, *Energy expenditure and indirect calorimetry in critical illness and convalescence: current evidence and practical considerations.* J Intensive Care, 2021. **9**(1): p. 8.
53. Weijs, P.J., et al., *Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study.* JPEN J Parenter Enteral Nutr, 2012. **36**(1): p. 60-8.
54. Nicolo, M., et al., *Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study.* JPEN J Parenter Enteral Nutr, 2016. **40**(1): p. 45-51.
55. Koekkoek, W., et al., *Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study.* Clin Nutr, 2019. **38**(2): p. 883-890.
56. Singer, P., et al., *ESPEN guideline on clinical nutrition in the intensive care unit.* Clin Nutr, 2019. **38**(1): p. 48-79.
57. Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* Lancet, 2020. **395**(10229): p. 1054-1062.
58. Grasselli, G., et al., *Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy.* JAMA Intern Med, 2020. **180**(10): p. 1345-1355.

Table 1. Characteristics of COVID-19 inpatients admitted to the intensive care unit (ICU) at Harborview Medical Center from March 5, 2020 to October 31, 2020 by invasive mechanical ventilation (IMV) status (N=95)

Variables	IMV[a] (N=48)	Non-IMV (N=47)	Overall (N=95)
Demographics			
Age (years)	57.9 (14.0)[b]	64.0 (17.6)	60.9 (16.1)
Male	42 (87.5%)	33 (70.2%)	75 (78.9%)
Race/Ethnicity			
Non-Hispanic White	11 (22.9%)	11 (23.4%)	22 (23.2%)
Hispanic	19 (39.6%)	22 (46.8%)	41 (43.2%)
Non-Hispanic Black	5 (10.4%)	3 (6.4%)	8 (8.4%)
Non-Hispanic Asian	6 (12.5%)	8 (17.0%)	14 (14.7%)
Non-Hispanic Others and Unknown	7 (14.6%)	3 (6.4%)	10 (10.5%)
Comorbidities			
BMI[c] (kg/m^2)	30.8 (6.19)	27.4 (6.30)	29.2 (6.4)
Categorical BMI (kg/m^2)			
Underweight [17.9,18.5]	0 (0.0%)	1 (2.1%)	1 (1.1%)
Normal [18.5,25.0)	8 (16.7%)	14 (29.8%)	22 (23.2%)
Overweight [25.0,30.0)	14 (29.2%)	18 (38.3%)	32 (33.7%)
Obesity [30.0,57.3)	26 (54.2%)	11 (23.4%)	37 (38.9%)
Unknown	0 (0.0%)	3 (6.4%)	3 (3.2%)
Type 2 Diabetes	20 (41.7%)	15 (31.9%)	35 (36.8%)
Hypertension	22 (45.8%)	23 (48.9%)	45 (47.4%)
COPD[d]	4 (8.3%)	4 (8.5%)	8 (8.4%)
CVD[e]	5 (10.4%)	10 (21.3%)	15 (15.8%)
Prior Medication Use			
ACEIs[f]	11 (22.9%)	10 (21.3%)	21 (22.1%)
ARBs[g]	6 (12.5%)	5 (10.6%)	11 (11.6%)
Statin	15 (31.2%)	13 (27.7%)	28 (29.5%)
SOFA Score[h]	5.0 (4.3)	2.4 (2.8)	3.7 (3.8)
ECMO	13 (27.1%)	0 (0%)	13 (13.7%)
Do-Not-Intubate	0 (0%)	18 (38.3%)	18 (18.9%)
In-Hospital Death	20 (41.7%)	12 (25.5%)	32 (33.7%)

[a] IMV: invasive mechanical ventilation through the endotracheal tube; [b] Continuous variables are presented as mean (standard deviation). Categorical variables are presented as count (percentage); [c] BMI: Body Mass Index; [d] COPD: Chronic Obstructive Pulmonary Disease; [e] CVD: Cardiovascular disease; [f] ACEIs: Angiotensin Converting Enzyme Inhibitors; [g] ARBs: Angiotensin II Receptor Blockers; [h] SOFA Score: Sequential Organ Failure Assessment Score

Figure 1. ICU Length of Stay (N=95)

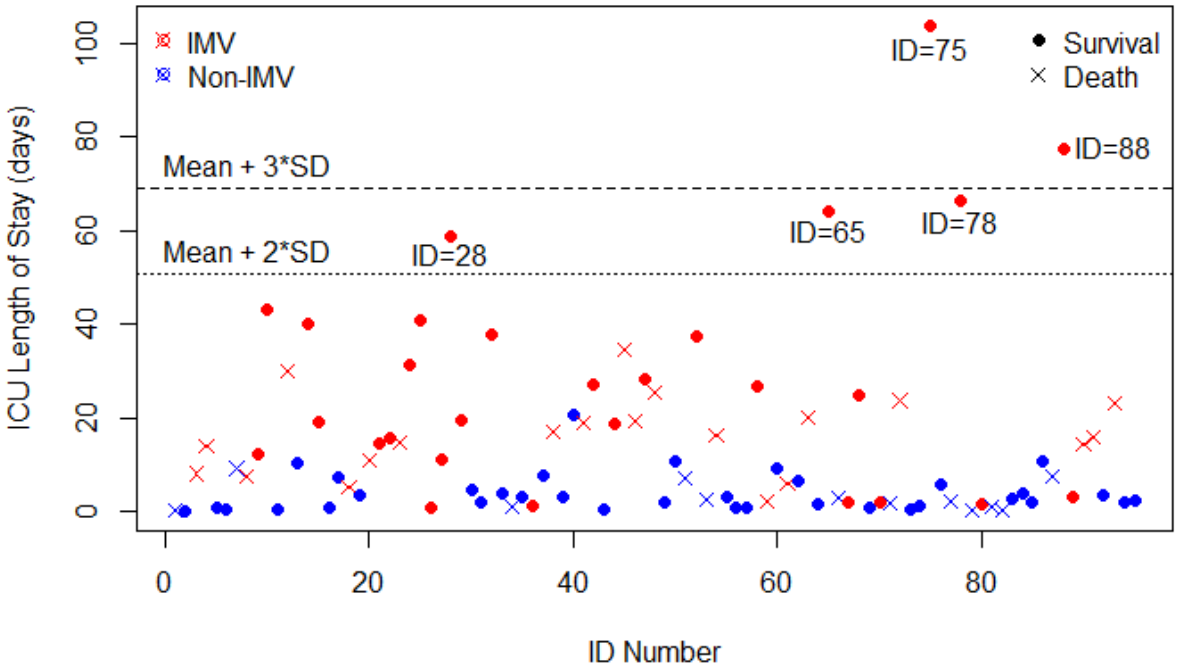

Table 2. Associations between invasive mechanical ventilation (IMV) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, prior medication use, and SOFA score in COVID-19 inpatients admitted to ICU at Harborview Medical Center; odds ratios (ORs), 95% confidence interval (CIs) and p-values from logistic regression models are shown. (N=95)

	Unadjusted models		Model 2[a]		Model 3[b]		Model 4[c]		Model 5[d]	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
IMV	2.08 (0.87,4.98)	0.099	3.28 (1.12,9.59)	0.030*	3.01 (0.97,9.39)	0.057	3.04 (0.96,9.58)	0.058	2.92 (0.84,10.15)	0.09
Demographics										
Age (yrs) 1 year older	1.04 (1.02,1.07)	0.002*	1.05 (1.02,1.09)	0.005*	1.07 (1.02,1.13)	0.005*	1.07 (1.02,1.13)	0.006*	1.07 (1.02,1.13)	0.009*
Sex Male vs. Female	0.93 (0.33,2.62)	0.89	0.74 (0.22,2.52)	0.63	0.89 (0.21,3.78)	0.88	0.85 (0.17,4.3)	0.840	0.82 (0.16,4.17)	0.81
Race/Ethnicity										
Non-Hispanic White	Ref.	-	Ref.	-	Ref.	-	Ref.	-	Ref.	-
Hispanic	0.52 (0.16,1.70)	0.28	0.94 (0.24,3.65)	0.93	0.82 (0.19,3.55)	0.79	0.81 (0.18,3.74)	0.79	0.82 (0.18,3.85)	0.80
Non-Hispanic Black	3.57 (0.66,19.34)	0.14	2.84 (0.4,20.25)	0.30	2.79 (0.38,20.38)	0.31	2.8 (0.37,20.97)	0.32	2.74 (0.37,20.41)	0.32
Non-Hispanic Asian	1.61 (0.40,6.44)	0.50	1.59 (0.36,7.05)	0.54	1.26 (0.25,6.22)	0.78	1.19 (0.2,7.03)	0.84	1.21 (0.2,7.36)	0.84
Non-Hispanic Others and Unknown	3.21 (0.68,15.16)	0.14	3.9 (0.66,23.16)	0.13	3.22 (0.37,28.05)	0.29	3.14 (0.37,27)	0.30	3 (0.36,25.02)	0.31
Comorbidities										
BMI (kg/m^2)										
Normal [18.5,25.0)	Ref.	-			Ref.	-	Ref.	-	Ref.	-
Overweight [25.0,30.0)	1.21 (0.37,4.02)	0.75			1.64 (0.35,7.78)	0.53	1.63 (0.33,8)	0.55	1.61 (0.33,7.91)	0.55
Obesity [30.0,57.3)	1.44 (0.45,4.59)	0.53			2.4 (0.59,9.85)	0.22	2.4 (0.56,10.23)	0.24	2.4 (0.56,10.29)	0.24
Unknown[e]	8.00 (0.69,92.70)	0.10			6.29 (0.27,144.67)	0.25	6.26 (0.22,181.97)	0.29	6.1 (0.2,182.52)	0.30
Type 2 Diabetes	2.32 (0.96,5.57)	0.06			2.63 (0.85,8.08)	0.09	2.7 (0.77,9.51)	0.12	2.71 (0.76,9.6)	0.12
Hypertension	1.42 (0.60,3.33)	0.42			0.51 (0.16,1.65)	0.26	0.54 (0.15,1.92)	0.34	0.56 (0.15,2.11)	0.39
COPD	2.11 (0.47,9.05)	0.32			0.94 (0.15,5.72)	0.94	0.91 (0.12,7.16)	0.93	0.93 (0.12,7.28)	0.95
CVD	1.38 (0.45,4.30)	0.57			0.58 (0.09,3.91)	0.58	0.58 (0.08,3.99)	0.58	0.57 (0.08,3.84)	0.56
Prior medication use										
ACEIs	2.15 (0.80,5.79)	0.13					1.06 (0.15,7.53)	0.95	1.02 (0.15,7.21)	0.98
ARBs	0.71 (0.18,2.89)	0.63					0.92 (0.15,5.56)	0.92	0.88 (0.14,5.71)	0.83
Statin	1.76 (0.71,4.40)	0.22					0.9 (0.2,3.98)	0.89	0.92 (0.2,4.17)	0.91
SOFA Score	1.10 (0.98,1.23)	0.10							1.02 (0.87,1.2)	0.83

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted for prior medication use; [d] Model 5: further adjusted for SOFA Score; [e] The only underweight patient (BMI=17.9) was grouped as Unknown for statistical reason.

Table 3. Associations between invasive mechanical ventilation (IMV) and ICU length of stay unadjusted and adjusted for demographics, comorbidities, prior medication use, and SOFA score in COVID-19 inpatients admitted to ICU who survived to discharge at Harborview Medical Center; β coefficients, 95% CIs and p-values from linear regression models are shown. (N=63)

	Unadjusted models		Model 2[a]		Model 3[b]		Model 4[c]		Model 5[d]	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
IMV	25.6 (16.2,35.1)	<0.001*	24.7 (16.5,32.9)	<0.001*	22.4 (15.3,29.4)	<0.001*	22.1 (15.1,29.1)	<0.001*	19.4 (11.6,27.3)	<0.001*
Demographics										
Age (yrs) 1 year older	-0.2 (-0.5,0.1)	0.15	-0.2 (-0.5,0.1)	0.22	-0.2 (-0.4,0.1)	0.13	-0.1 (-0.3,0.1)	0.39	-0.1 (-0.3,0.2)	0.53
Sex Male vs. Female	7.5 (-4.9,19.9)	0.23	-1.5 (-14.9,11.9)	0.83	0.6 (-10.9,12.2)	0.91	6.1 (-5.6,17.8)	0.31	4.3 (-6.5,15.2)	0.44
Race/Ethnicity										
Non-Hispanic White	Ref.	-	Ref.	-	Ref.	-	Ref.	-	Ref.	-
Hispanic	-1.4 (-13.1,10.3)	0.82	-0.4 (-11.4,10.6)	0.94	-4.3 (-17.1,8.6)	0.51	-4.9 (-13.9,4.2)	0.30	-2.4 (-11.7,7)	0.62
Non-Hispanic Black	-1.8 (-24.7,21.2)	0.88	-4.1 (-25.3,17.1)	0.70	6.7 (-13.6,26.9)	0.52	6.2 (-10.3,22.6)	0.46	6.4 (-13.3,26)	0.53
Non-Hispanic Asian	-11.9 (-22.4,-1.4)	0.03*	-10.8 (-27.8,6.1)	0.21	-13.7 (-31.8,4.4)	0.14	-17.9 (-35.3,-0.5)	0.04*	-13.6 (-31.5,4.2)	0.13
Non-Hispanic Others and Unknown	28.3 (-14.2,70.9)	0.19	28.5 (-1.4,58.4)	0.06	27.1 (-1.5,55.7)	0.06	32.7 (8.5,56.9)	0.008*	30.7 (9.3,52)	0.005*
Comorbidities										
BMI (kg/m^2)										
Normal [18.5,25.0)	Ref.	-			Ref.	-	Ref.	-	Ref.	-
Overweight [25.0,30.0)	2 (-6.3,10.4)	0.64			1.7 (-6.3,9.7)	0.68	2.5 (-5,10)	0.51	2.3 (-5.1,9.7)	0.54
Obesity [30.0,57.3)	15.4 (3.2,27.7)	0.01*			8.2 (-0.5,16.9)	0.06	6.9 (-2.7,16.5)	0.16	7.4 (-2.1,16.9)	0.13
Unknown[e]	-8.6 (-13.9,-3.2)	0.002*			11.5 (-4.3,27.3)	0.16	24.3 (-1.2,49.8)	0.06	17 (-7.6,41.6)	0.18
Type 2 Diabetes	0.9 (-13.3,15.2)	0.90			0.2 (-9.7,10)	0.97	1.4 (-9.7,12.6)	0.80	1.2 (-9.3,11.6)	0.83
Hypertension	-0.8 (-11.4,9.7)	0.88			4.9 (-4.1,13.9)	0.29	2.1 (-6.8,11.1)	0.64	3.1 (-6,12.1)	0.51
COPD	-12.5 (-19.4,-5.6)	<0.001*			-15.5 (-38.9,7.8)	0.19	-16.5 (-36.2,3.1)	0.10	-14.4 (-35.8,7)	0.19
CVD	-8.3 (-17.8,1.3)	0.09			-5.2 (-19.1,8.7)	0.46	-6 (-18.1,6.1)	0.33	-6.8 (-18.7,5.1)	0.26
Prior medication use										
ACEIs	-1 (-15.5,13.6)	0.90					6.7 (-10.1,23.4)	0.43	5.6 (-10.7,21.9)	0.50
ARBs	6.3 (-15,27.5)	0.56					20.3 (2.1,38.5)	0.03*	17.5 (-0.2,35.2)	0.05
Statin	0.2 (-12.7,13)	0.98					-11.5 (-29.9,7)	0.22	-10.3 (-27.3,6.6)	0.23
SOFA Score	2.7 (1,4.4)	0.002*							0.9 (-0.2,2)	0.10

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted for prior medication use; [d] Model 5: further adjusted for SOFA Score; [e] The only underweight patient (BMI=17.9) was grouped as Unknown for statistical reason.

Figure 2. Length on IMV Among Ventilated Patients (N=48)

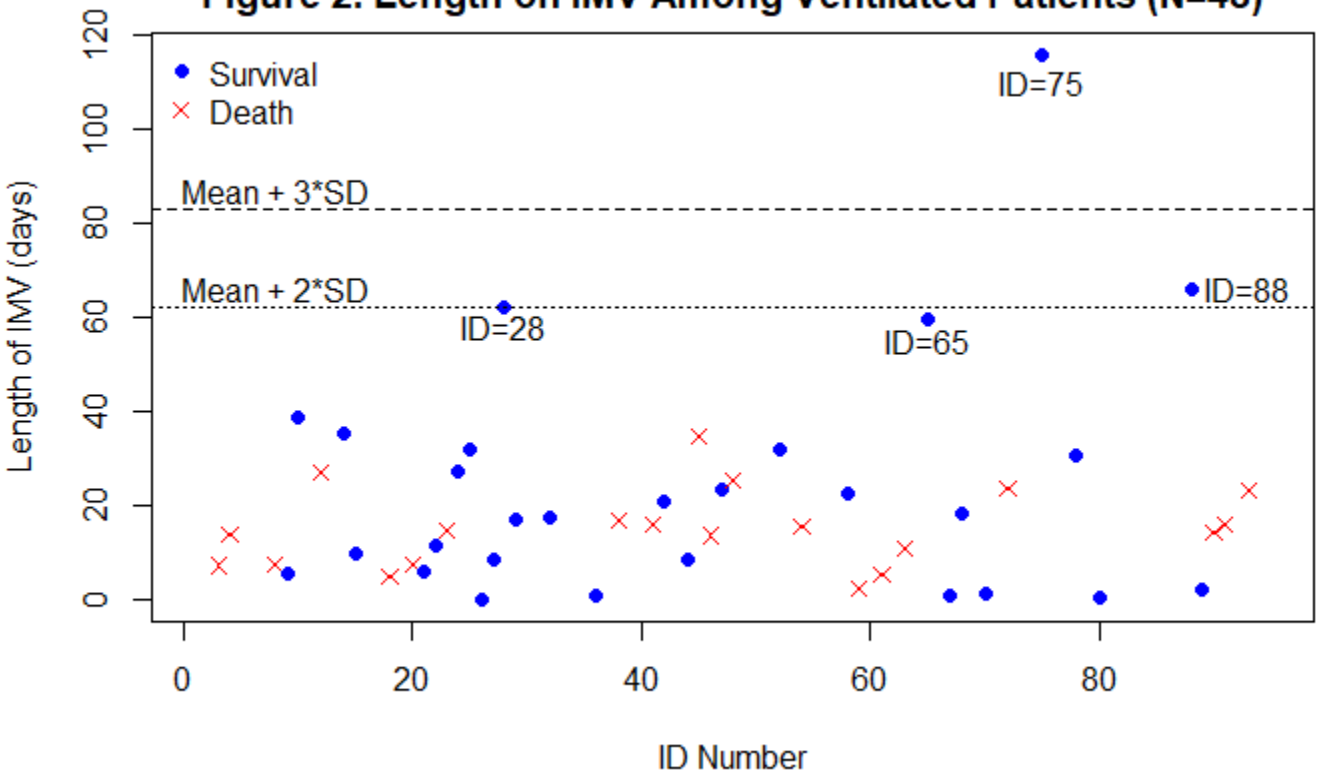

Table 4. Characteristics of IMV COVID-19 inpatients admitted to ICU at Harborview Medical Center from March 5, 2020 to October 31, 2020 by mortality status (N=43[a])

Variables	Death (N=19)	Survivor (N=24)	Overall (N=43)
Length on IMV (d)	14.5 (8.4)	28.0 (26.1)	22.0 (21.2)
Nutrition intake			
Energy Intake per Day (kcal/d)	1879.3 (458.8)	1904.5 (388.9)	1890 (416.2)
Energy Intake per Goal (%)	91.4 (19.4)	95.0 (15.0)	93.4 (16.9)
Energy Intake per IBW (kcal/kg/d)	26.5 (6.4)	27.2 (4.5)	26.9 (5.4)
Energy from propofol (%)	20.9 (9.9)	20.1 (13.6)	20.5 (11.9)
Protein Intake per Day (g/d)	79.6 (23.3)	85.6 (19.2)	82.9 (21.1)
Protein Intake per Goal (%)	62.4 (15.6)	70.6 (17.0)	66.9 (16.7)
Protein Intake per IBW (g/kg/d)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)
Demographics			
Age (years)	61.3 (11.2)	54.0 (16.1)	57.2 (14.5)
Male	16 (84.2%)	21 (87.5%)	37 (86.0%)
Race/Ethnicity			
Non-Hispanic White	3 (15.8%)	7 (29.2%)	10 (23.3%)
Others	14 (73.7%)	15 (62.5%)	29 (67.4%)
Unknown	2 (10.5%)	2 (8.3%)	4 (9.3%)
Comorbidities			
BMI (kg/m^2)	31.1 (5.6)	31.6 (6.4)	31.4 (6.0)
Categorical BMI (kg/m^2)			
Normal [18.5,25.0)	2 (10.5%)	4 (16.7%)	6 (14.0%)
Overweight [25.0,30.0)	6 (31.6%)	6 (25.0%)	12 (27.9%)
Obesity [30.0,57.3)	11 (57.9%)	14 (58.3%)	25 (58.1%)
Type 2 Diabetes	11 (57.9%)	6 (25.0%)	17 (39.5%)
Hypertension	11 (57.9%)	8 (33.3%)	19 (44.2%)
COPD	2 (10.5%)	0 (0%)	2 (4.7%)
CVD	2 (10.5%)	3 (12.5%)	5 (11.6%)
Prior medication use			
ACEIs	5 (26.3%)	4 (16.7%)	9 (20.9%)
ARBs	3 (15.8%)	2 (8.3%)	5 (11.6%)
Statin	8 (42.1%)	5 (20.8%)	13 (30.2%)
SOFA Score	4.6 (3.4)	5.2 (5.1)	4.9 (4.4)
ECMO[b]	5 (26.3%)	7 (29.2%)	12 (27.9%)

[a] Five patients had too short length on IMV (<24h) to receive enteral nutrition, thus were excluded from the analysis; [b] ECMO: received extracorporeal membrane oxygenation during IMV.

Table 5. Associations between energy intake per ideal body weight (IBW) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, SOFA score, and ECMO among invasive mechanical ventilated COVID-19 inpatients admitted to ICU at Harborview Medical Center (N=43)

Variables	Unadjusted Models		Model 2[a]		Model 3[b]		Model 4[c]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Energy intake per IBW								
1 kcal/kg/d higher	0.97 (0.86,1.1)	0.66	0.95 (0.85,1.06)	0.36	0.93 (0.82,1.05)	0.22	0.91 (0.8,1.03)	0.13
Demographics								
Age (yrs) 1 year older	1.04 (0.99,1.09)	0.12	1.06 (1,1.12)	0.04*	1.07 (1.01,1.14)	0.02*	1.1 (1.01,1.2)	0.03*
Sex Male vs. Female	0.76 (0.14,4.29)	0.76	0.43 (0.09,2.05)	0.29	0.71 (0.1,4.98)	0.73	0.52 (0.06,4.8)	0.56
Race/Ethnicity								
Non-Hispanic White	Ref.	-	Ref.	-	Ref.	-	Ref.	-
Others	2.18 (0.47,10.12)	0.32	3.3 (0.55,19.86)	0.19	5.08 (0.48,53.56)	0.18	7.86 (0.88,70.5)	0.06
Unknown	2.33 (0.22,25.24)	0.49	7.68 (0.47,124.3)	0.15	9.3 (0.17,496.34)	0.27	19.89 (0.48,831.03)	0.11
Comorbidities [f]								
BMI (kg/m^2)								
Normal [18.5,25.0)	Ref.	-			Ref.	-	Ref.	-
Overweight [25.0,30.0)	2.00 (0.26,15.38)	0.50			7.28 (0.71,74.43)	0.09	5.96 (0.34,103.52)	0.22
Obesity [30.0,57.3)	1.57 (0.24,10.22)	0.64			3.14 (0.4,24.6)	0.28	3.62 (0.33,40.04)	0.30
Type 2 Diabetes	4.12 (1.13,15.1)	0.03*			6.44 (1.32,31.53)	0.02*	7.89 (1.46,42.49)	0.02*
Hypertension	2.75 (0.79,9.55)	0.11			1.56 (0.24,10.19)	0.64	1.33 (0.17,10.58)	0.79
CVD	0.82 (0.12,5.51)	0.84			0.2 (0.01,4.15)	0.30	0.34 (0.02,7.49)	0.49
SOFA Score	0.97 (0.85,1.1)	0.62					0.97 (0.78,1.22)	0.82
ECMO	0.87 (0.23,3.34)	0.84					3.64 (0.41,32.11)	0.24

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted for SOFA Score and ECMO; [f] COPD was excluded due to lack of cases.

Table 6. Associations between protein intake per ideal body weight (IBW) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, SOFA score, and ECMO among invasive mechanical ventilated COVID-19 inpatients admitted to ICU at Harborview Medical Center (N=43)

Variables	Unadjusted Models		Model 2[a]		Model 3[b]		Model 4[c]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Protein intake per IBW								
0.1 g/kg/d higher	0.89 (0.72, 1.09)	0.27	0.82 (0.65, 1.03)	0.08	0.79 (0.56,1.11)	0.17	0.54 (0.34,0.87)	0.01*
Demographics								
Age (yrs) 1 year older	1.04 (0.99,1.09)	0.12	1.07 (1.01,1.14)	0.03*	1.07 (1.01,1.14)	0.02*	1.16 (1.06,1.27)	0.001*
Sex Male vs. Female	0.76 (0.14,4.29)	0.76	0.47 (0.09,2.42)	0.36	1.12 (0.16,8.1)	0.91	0.97 (0.06,15.63)	0.98
Race/Ethnicity								
Non-Hispanic White	Ref.	-	Ref.	-	Ref.	-	Ref.	-
Others	2.18 (0.47,10.12)	0.32	3.29 (0.61,17.56)	0.16	5.4 (0.59,49.82)	0.14	34.37 (4.03,292.98)	0.001*
Unknown	2.33 (0.22,25.24)	0.49	8.03 (0.59,109.64)	0.12	10.4 (0.27,394.25)	0.21	228.28 (3.66,14251.78)	0.01*
Comorbidities								
BMI (kg/m^2)								
Normal [18.5,25.0)	Ref.	-			Ref.	-	Ref.	-
Overweight [25.0,30.0)	2.00 (0.26,15.38)	0.50			8.10 (0.67,98.04)	0.10	7.00 (0.21,231.57)	0.28
Obesity [30.0,57.3)	1.57 (0.24,10.22)	0.64			2.22 (0.27,18.04)	0.46	2.27 (0.16,32.39)	0.54
Type 2 Diabetes	4.12 (1.13,15.1)	0.03*			5.53 (1.18,25.96)	0.03*	8.85 (1.39,56.43)	0.02*
Hypertension	2.75 (0.79,9.55)	0.111			1.81 (0.25,13.29)	0.559	2.83 (0.22,36.87)	0.43
CVD	0.82 (0.12,5.51)	0.84			0.22 (0.01,5.4)	0.35	0.67 (0.03,14.53)	0.800
SOFA Score	0.97 (0.85,1.1)	0.62					0.96 (0.77,1.21)	0.73
ECMO	0.87 (0.23,3.34)	0.84					55.69 (2.76,1124.34)	0.009*

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted for SOFA Score and ECMO.

Table 7. Associations between nutrition intakes per ideal body weight (IBW) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, SOFA score, and ECMO among mechanical ventilated COVID-19 inpatients admitted to ICU at Harborview Medical Center (N=43)

Variables	Unadjusted Models		Model 2[a]		Model 3[b]		Model 4[c]		Model 5[d]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Nutrition intakes										
Energy Intake per IBW										
1 kcal/kg/d higher	0.97 (0.86,1.1)	0.66	1.05 (0.88,1.24)	0.59	1.07 (0.9,1.27)	0.44	1.02 (0.83,1.25)	0.83	1.1 (0.87,1.4)	0.43
Protein Intake per IBW										
0.1 g/kg/d higher	0.89 (0.72, 1.09)	0.27	0.84 (0.62,1.13)	0.25	0.75 (0.52,1.08)	0.12	0.77 (0.46,1.28)	0.31	0.47 (0.23,0.98)	0.04*
Demographics										
Age (yrs) 1 year older	1.04 (0.99,1.09)	0.12			1.07 (1.01,1.14)	0.03*	1.07 (1.01,1.14)	0.02*	1.17 (1.06,1.29)	0.002*
Sex Male vs. Female	0.76 (0.14,4.29)	0.76			0.48 (0.09,2.64)	0.40	1.16 (0.16,8.67)	0.89	1.24 (0.08,18.5)	0.88
Race/Ethnicity										
Non-Hispanic White	Ref.	-			Ref.	-	Ref.	-	Ref.	-
Others	2.18 (0.47,10.12)	0.32			3.01 (0.59,15.33)	0.18	5.19 (0.56,47.96)	0.15	30.81 (3.82,248.21)	0.001*
Unknown	2.33 (0.22,25.24)	0.49			6.95 (0.57,83.99)	0.13	9.78 (0.26,366.09)	0.22	227.13 (2.92,17651.64)	0.02*
Comorbidities										
BMI (kg/m^2)										
Normal [18.5,25.0)	Ref.	-					Ref.	-	Ref.	-
Overweight [25.0,30.0)	2.00 (0.26,15.38)	0.50					7.87 (0.71,87.81)	0.09	5.85 (0.2,170.76)	0.30
Obesity [30.0,57.3)	1.57 (0.24,10.22)	0.64					2.24 (0.28,17.6)	0.44	2.3 (0.18,29.67)	0.52
Type 2 Diabetes	4.12 (1.13,15.1)	0.03*					5.45 (1.17,25.49)	0.03*	8.43 (1.24,57.19)	0.03*
Hypertension	2.75 (0.79,9.55)	0.11					1.76 (0.25,12.45)	0.57	2.77 (0.2,37.85)	0.44
CVD	0.82 (0.12,5.51)	0.84					0.22 (0.01,5.12)	0.35	0.83 (0.04,15.82)	0.90
SOFA Score	0.97 (0.85,1.1)	0.62							0.95 (0.76,1.2)	0.69
ECMO	0.87 (0.23,3.34)	0.84							76.39 (2.46,2371.32)	0.01*

[a] Model 2: include both energy and protein intake as exposures; [b] Model 3: adjusted for demographics; [c] Model 4: further adjusted for comorbidities; [d] Model 5: further adjusted for SOFA Score and ECMO.

[Appendix]: Sensitivity analyses

A. Exclude patients with ICU length of stay > mean + 3SD (exclude ID number: 75, 88)

Table 1. Associations between invasive mechanical ventilation (IMV) and ICU length of stay unadjusted and adjusted for demographics, comorbidities, prior medication use, and SOFA score in COVID-19 inpatients admitted to ICU who survived to discharge at Harborview Medical Center; β coefficients, 95% CIs and p-values from linear regression models are shown. (N=61)

	Unadjusted models		Model 2[a]		Model 3[b]		Model 4[c]		Model 5[d]	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
IMV	21.0 (13.5,28.4)	<0.001*	20.6 (13.8,27.5)	<0.001*	19.5 (13.2,25.8)	<0.001*	19.97 (13.6,26.1)	<0.001*	18.7 (12.0,25.5)	<0.001*

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted for prior medication use; [d] Model 5: further adjusted for SOFA Score; [e] The only underweight patient (BMI=17.9) was grouped as Unknown for statistical reason.

B. Exclude patients with length on IMV > mean + 3SD (exclude ID number: 75)

Table 2. Associations between energy intake per ideal body weight (IBW) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, SOFA score, and ECMO among invasive mechanical ventilated COVID-19 inpatients admitted to ICU at Harborview Medical Center (N=43)

Variables	Unadjusted Models		Model 2[a]		Model 3[b]		Model 4[c]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Energy intake per IBW								
1 kcal/kg/d higher	0.97 (0.86,1.09)	0.64	0.94 (0.84,1.06)	0.31	0.93 (0.83,1.05)	0.25	0.91 (0.8,1.03)	0.13

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted for SOFA score and ECMO.

Table 3. Associations between protein intake per ideal body weight (IBW) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, SOFA score, and ECMO among invasive mechanical ventilated COVID-19 inpatients admitted to ICU at Harborview Medical Center (N=43)

Variables	Unadjusted Models		Model 2[a]		Model 3[b]		Model 4[c]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Protein intake per IBW								
0.1 g/kg/d higher	0.89 (0.72, 1.09)	0.26	0.81 (0.64, 1.03)	0.08	0.81 (0.58,1.14)	0.22	0.57 (0.36,0.91)	0.02*

[a] Model 2: adjusted for demographics; [b] Model 3: further adjusted for comorbidities; [c] Model 4: further adjusted SOFA score and ECMO.

Table 4. Associations between nutrition intakes per ideal body weight (IBW) and risk of in-hospital mortality unadjusted and adjusted for demographics, comorbidities, SOFA score, and ECMO among invasive mechanical ventilated COVID-19 inpatients admitted to ICU at Harborview Medical Center (N=43)

Variables	Unadjusted Models		Model 2[a]		Model 3[b]		Model 4[c]		Model 5[d]	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Energy Intake per IBW										
1 kcal/kg/d higher	0.97 (0.86,1.09)	0.64	1.05 (0.88,1.24)	0.60	1.06 (0.89,1.27)	0.49	1.02 (0.81,1.29)	0.85	1.09 (0.85,1.41)	0.50
Protein Intake per IBW										
0.1 g/kg/d higher	0.89 (0.72, 1.09)	0.26	0.84 (0.62, 1.13)	0.25	0.75 (0.52,1.08)	0.12	0.79 (0.46,1.35)	0.39	0.51 (0.25,1.02)	0.06

[a] Model 2: include both energy and protein intake as exposures; [b] Model 3: adjusted for demographics; [c] Model 4: further adjusted for comorbidities; [d] Model 5: further adjusted SOFA score and ECMO.