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Early Enteral Nutrition in Mechanically Ventilated Patients With COVID-19 Infection

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Abstract

Background: Nutrition therapy is essential in critically ill adults. Little is known about appropriate nutrition therapy in patients with severe coronavirus disease 2019 (COVID-19) infection. *Methods:* This was a retrospective, observational study in adult patients with confirmed COVID-19 infection receiving mechanical ventilation. Data regarding patient demographics and nutrition therapy were collected. Patients that received enteral nutrition within 24 hours of starting mechanical ventilation were compared with patients starting enteral nutrition later. The primary outcome was inpatient length of stay. Propensity score matching was conducted to control for baseline differences in patient groups. *Results:* One hundred fifty-five patients were included in final analysis. Patients who received enteral nutrition within 24 hours received a significantly greater daily amount of calories (17.5 vs 15.2 kcal/kg, $P = .015$) and protein (1.04 vs 0.85 g/kg, $P = .003$). There was no difference in length of stay (18.5 vs 23.5 days, $P = .37$). The propensity score analysis included 100 patients. Following propensity scoring, significant differences in daily calorie (17.7 [4.6] vs 15.1 [5.1] kcal/kg/d, $P = .009$) and protein (1.03 [0.35] vs 0.86 [0.38] g/kg/d, $P = .014$) provision remained. No differences in length of stay or other outcomes were noted in the propensity score analysis. *Conclusion:* Initiation of enteral nutrition within 24 hours was not associated with improved outcomes in mechanically ventilated adults with COVID-19. No harm was detected either. Future research should seek to clarify optimal timing of enteral nutrition initiation in patients with COVID-19 who require mechanical ventilation. (*Nutr Clin Pract.* 2021;36:440–448)

Keywords

COVID-19; critical care; enteral nutrition; length of stay; mechanical ventilation; SARS-CoV-2

Introduction

Nutrition therapy plays an important role in the management of critically ill patients. Significant delay in initiation of enteral nutrition with accumulation of caloric deficit has been associated with more nosocomial infections, longer length of stay, and higher mortality.[1–3, 4] Enteral nutrition is the delivery route of choice, as it promotes gut integrity and reduces systemic inflammation when compared with parenteral nutrition.[5,6] Guidelines recommend initiation of enteral nutrition within 24–48 hours of onset of critical illness in patients who cannot take in nutrition orally on their own.[7,8]

Although early nutrition intervention is widely accepted as standard of care, much is unknown about optimal nutrition therapy practices. Although some studies have found that early, aggressive calorie provision via enteral nutrition is beneficial, other studies have demonstrated that trophic or hypocaloric feeding may yield similar outcomes.[9,10] Early use of parenteral nutrition to meet 100% of caloric goals has not been shown to significantly improve outcomes.[11,12] The optimal amount of nutrition provision is especially controversial in patients with acute respiratory distress syndrome and acute lung injury (ALI). One randomized controlled trial in patients with ALI found no benefit to full enteral nutrition as opposed to trophic feeding for the first 6 days of mechanical ventilation.[13] Another randomized controlled

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trial in patients with ALI was terminated early because full nutrition was associated with higher mortality.[14]

Like many other therapeutic modalities, the role of nutrition intervention in critically ill patients with coronavirus disease 2019 (COVID-19) is poorly understood. Previous literature in ALI suggests that early, goal enteral nutrition does not improve outcomes. However, others have suggested that because of the severity of inflammation and illness observed in patients with COVID-19, risk of acquiring malnutrition may be higher.[15] Additionally, patients with COVID-19 may have had poor oral intake for days prior to admission. Statements from nutrition societies have recommended early consideration of parenteral nutrition in patients with COVID-19 who cannot tolerate enteral nutrition.[16,17] The objective of this study was primarily to associate provision of early enteral nutrition with outcomes in mechanically ventilated patients with COVID-19 and secondarily to describe practical nutrition practices in mechanically ventilated patients with COVID-19.

Methods

This retrospective observational study was conducted at a single tertiary academic medical center. Patients were included if they were primarily admitted for COVID-19 pneumonia between March 1, 2020, and May 1, 2020, and required mechanical ventilation. Active COVID-19 infection was confirmed by positive polymerase chain reaction test results on admission. Patients who were mechanically ventilated for >48 hours at an outside institution prior to transfer were excluded. Patients that were mechanically ventilated for <48 hours and patients in whom nutrition provision was unable to be accurately collected retrospectively from the medical record were also excluded. This studied was approved by the University of Michigan Institutional Review Board with waiver of informed consent (HUM 00181,276).

Institutional recommendations for nutrition support in critically ill patients with COVID-19 were established and disseminated early during the response to the pandemic. However, critically ill patients with COVID-19 were not managed via a nutrition support team or universal protocol. Decisions to initiate or hold nutrition therapy and how much enteral nutrition to provide were at the discretion of the multidisciplinary medical team caring for the patient. Each multidisciplinary team included a registered dietitian who evaluated the patients and made nutrition recommendations. Open-label remdesivir was not readily available at the study institution during the study period. Additionally, early corticosteroids were not routinely administered for respiratory indications during the study period.

Patient demographic information, including age, sex, and relevant baseline comorbidities, were collected. Dietitians assessed the nutrition status of all patients at baseline, when possible. A diagnosis of nonsevere or severe malnutrition was made based on a local assessment tool adapted from American Society for Parenteral and Enteral Nutrition (ASPEN)/Academy of Nutrition and Dietetics criteria.[18] Presentation with gastrointestinal symptoms of COVID-19, including nausea, diarrhea, and lack of appetite, was recorded. Days of fever in the first 7 days of mechanical ventilation were likewise recorded. To assess severity of illness, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, Sequential Organ Failure Assessment (SOFA) scores, and ratios of partial pressure of oxygen to fraction of inspired oxygen (P:F) were calculated for each patient, using the most aberrant data points in the 24 hours following the start of mechanical ventilation at the study institution.[19,20] Other therapies used in the treatment of COVID-19 were recorded, including prone positioning, neuromuscular blockade, tocilizumab, inhaled nitric oxide, and vevo-venous extracorporeal membrane oxygenation (ECMO). Enrollment in a clinical trial for an experimental therapy for COVID-19 was also recorded.

Nutrition provision was recorded for the first 7 days following start of mechanical ventilation. Each day was defined as an individual calendar day from midnight to midnight. Total calorie intake from enteral nutrition, protein supplements, intravenous (IV) lipids via propofol, IV continuous dextrose infusions, and parenteral nutrition was totaled each day. Total protein intake was also calculated each day. Concomitant use of enteral nutrition and vasopressor administration was recorded, in addition to instances of bowel ischemia within 24 hours of these concomitant therapies. Owing to staffing limitations and limits of staff exposure to patients, calorie intake was not recorded in patients that were able to tolerate a diet within the first 7 days following mechanical ventilation. Use of a prokinetic medication, defined as metoclopramide or erythromycin, was recorded. Days of severe hypophosphatemia (defined as a serum phosphorous level below 2 mg/dL) were recorded. Days with hyperglycemia (defined as a blood glucose reading >180 mg/d) and days with hypoglycemia (defined as a blood glucose reading <70 mg/dL) were recorded as well. Blood glucose levels were obtained from serum values, point-of-care readings, or blood gases. For patients receiving IV vitamin C, point-of-care readings were disregarded owing to inaccuracies in readings. Ideal body weight was calculated using the Hamwi method. For this analysis, weight-based daily provision of calories and protein was calculated using ideal body weight for all patients. In clinical practice, registered dietitians recommended weight-based protein and calorie goals using ideal, actual, or adjusted weight based on clinical judgement. Modified Nutrition Risk in Critically Ill (NUTRIC) scores were also retrospectively calculated for all patients using laboratory values drawn within 24 hours after initiation of mechanical ventilation; all modified NUTRIC scores were conducted without incorporating interleukin-6.[21]

Outcomes were compared between patients who received enteral nutrition within the first 24 hours of starting mechanical ventilation at the study institution and patients who initiated enteral nutrition at a later time. The primary outcome of the study was to compare inpatient length of stay in patients in whom enteral nutrition was initiated within the first 24 hours of mechanical ventilation vs patients with later initiation. Secondary outcomes were measured at 60 days after admission and included inpatient mortality, days alive and free of mechanical ventilation, tracheostomy, and discharge on oxygen in patients who received enteral nutrition within the first 24 hours of mechanical ventilation compared with patients with later initiation.[16] Additionally, patients were compared based on receipt of at least 15 kcal/kg/d (using ideal body weight) of nutrition vs <15 kcal/kg/d. The value of 15 kcal/kg/d was chosen because it has been suggested as a possible minimum calorie target for patients in the acute phase of critical illness.[22] Inpatient length of stay, inpatient mortality, days alive and free of mechanical ventilation, tracheostomy, and discharge on oxygen were also compared between patients who received at least 15 kcal/kg/d and patients who received <15 kcal/kg/d.

All statistical analyses were conducted using SPSS 26 (Armonk, NY). Baseline characteristics were analyzed using descriptive statistics. Continuous variables were evaluated using Student *t*-test and Mann-Whitney *U* test as appropriate based on normalcy of distribution. Nominal variables were compared using a χ^2 test or Fisher exact test. To control for baseline differences between groups, propensity score matching was performed. Propensity score matching controlled for any of the following variables if the *P*-value was <.1 when groups were compared at baseline: APACHE II, SOFA, age, body mass index, neuromuscular blockade, tocilizumab, prone positioning, and ECMO. These variables were selected because differences either likely predisposed patients to a poor outcome or indicated a higher severity of illness. Patients were included in the final propensity score analysis based on a match tolerance of 0.1. After propensity score matching was completed, 100 patients were included for analysis. Following propensity score matching, no differences were found for standardized mean differences and each covariate assessed.

Results

A total of 162 patients were included in the study. Six patients were excluded because they were mechanically ventilated for <48 hours, and 1 patient was excluded because of missing data, leaving 155 patients for final analysis. Patient demographics are represented in Table 1. A clear diagnosis of malnutrition was rarely made at the time of initiating mechanical ventilation, owing to a lack of information regarding prior energy intake or nutrition-focused physical findings. The majority (72.9%, n = 113) of patients had a modified NUTRIC score of ≥5, indicating that they were at a high nutrition risk during admission. Data regarding treatment location and admission type can be found in the supplementary appendix.

Practices describing nutrition provision are displayed in Table 2. Enteral nutrition was started within 24 hours in 38.7% (n = 60) of the 155 patients and within 48 hours in 69.7% (n = 108) of the patients. While mechanically ventilated, patients received a mean of 16.1 (SD 5.5) kcal/kg/d from all sources and 0.93 (SD 0.38) g/kg/d protein. Enteral nutrition was administered to 75.8% (n = 116) of patients while a vasopressor infusion was concurrently administered, with no documented instances of bowel ischemia or emergent operations due to suspicion of bowel ischemia. No patients began parenteral nutrition within the first 7 days of mechanical ventilation. Hyperglycemia was common, occurring in 78.7% (n = 122) of patients.

Patient outcomes are shown in Table 3. During the admission, 27.1% (42/155) patients died. Median inpatient length of stay was 22.0 (interquartile range, 23.8) days. A tracheostomy was performed in 16.8% (26/155) of patients, and 26.5% (41/155) of patients were discharged on a new oxygen requirement. Only 40% (62/155) of patients were discharged home.

To assess the role of early nutrition, patients were divided by receipt of enteral nutrition within 24 hours of starting mechanical ventilation or after. The results of this comparison are shown in Table 4. Patients who received enteral nutrition within 24 hours of starting mechanical ventilation received significantly more weight-based calories (17.5 [4.7] vs 15.2 [5/8] kcal/kg/d, *P* = .015) and protein (1.04 [0.35] vs 0.85 [0.39] g/kg/d, *P* = .003) daily. In patients who began enteral nutrition within 24 hours of mechanical ventilation, APACHE II scores (23.4 [6.4] vs 26.8 [7.5], *P* = .005) and SOFA scores (9.0 [2.8] vs 10.3 [3.1], *P* = .006) were significantly lower. The results of a propensity-matched analysis are shown in Table 5. Significant differences in daily calorie (17.7 [4.6] vs 15.1 [5.1] kcal/kg/d, *P* = .009) and protein (1.03 [0.35] vs 0.86 [0.38] g/kg/d, *P* = .014) provision were still present after propensity score matching. Initiating enteral nutrition within 24 hours of mechanical ventilation was not associated with a difference in length of stay (18.5 [25.0] vs 24.6 [20.6] days, *P* = .136). Inpatient mortality (28% (14/50) vs 22% (11/50), *P* = .644), days alive and free of mechanical ventilation (31.4 [22.4] vs 35.3 [20.0] days, *P* = .36), and the proportion of patients discharged home (40% (20/50) vs 50% (25/50), *P* = .422) also did not differ between groups. Moreover, administration of enteral nutrition within 24 hours was not associated with more days of hyperglycemia (4.3 [2.5] vs 3.5 [2.7] days, *P* = .129) or number of patients that developed severe hypophosphatemia (24% (12/50) vs 12% (6/50), *P* = .192). A similar analysis was conducted comparing patients

TABLE 1. Baseline Characteristics.

Characteristics	n = 155
Age, mean (SD)	60.3 (13.8)
Male, n (%)	103 (66.5)
Weight, kg, median (IQR)	98.5 (34.3)
BMI, median (IQR)	33.2 (12.6)
Comorbidities	
Chronic obstructive pulmonary disease, n (%)	17 (11.0)
Asthma, n (%)	23 (14.8)
Diabetes, n (%)	85 (54.9)
Prediabetes, n (%)	8 (5.2)
Hypertension, n (%)	113 (72.9)
Chronic kidney disease, n (%)	36 (23.2)
End-stage renal disease, n (%)	4 (2.6)
Immunocompromised, n (%)	21 (13.5)
Presentation with GI symptoms, n (%)	44 (28.3)
Temperature $\geq$ 38.3 °C for at least 1 d, n (%)	105 (67.7)
PaO_2/FiO_2 ratio, median (IQR)	128 (80)
PaO_2/FiO_2 ratio < 100, n (%)	44 (28.4)
APACHE II, mean (SD)	25.5 (7.3)
SOFA, mean (SD)	9.9 (3.1)
Serum albumin level, g/dL, median (IQR)	3.2 (0.6)
Modified NUTRIC $\geq$ 5, n (%)	113 (72.9)
Unclear nutrition status	152 (98.1)
Diagnosis of nonsevere malnutrition	3 (1.9)
Diagnosis of severe malnutrition	0 (0)

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; FiO_2, fraction of inspired oxygen; GI, gastrointestinal; IQR, interquartile range; NUTRIC, Nutrition Risk in Critically Ill; PaO_2, partial pressure of oxygen; SOFA, Sequential Organ Failure Assessment.

that received at least 15 kcal/kg/d of total calories with those receiving less, with no difference in outcomes found. Results of this analysis can be found in supplementary appendix.

Discussion

In this retrospective study of mechanically ventilated patients with COVID-19 pneumonia, patients presented with a high severity of illness, as evidenced by high baseline APACHE II and SOFA scores in addition to low P:F ratios. Over 70% of patients had a modified NUTRIC score of $\geq$5, which indicates that they may particularly benefit from aggressive nutrition therapy. Despite this, initiation of nutrition support within 24 hours of mechanical ventilation was not associated with improved clinical outcomes.

The results of this study conflict with previously published data. A meta-analysis conducted by Marik and colleagues demonstrated that early enteral nutrition was associated with fewer infectious complications and a reduction in inpatient length of stay.[2] Similarly, Doig et al also demonstrated a reduction in pneumonia and mortality when enteral nutrition was started within 24 hours, in a separate meta-analysis.[1] Both of these meta-analyses primarily included studies conducted in surgical and trauma patients. Medical patients, such as those with COVID-19, may not derive a similar benefit from very early nutrition. Although less than half of the overall cohort was fed within 24 hours of mechanical ventilation, nearly 70% of patients started enteral nutrition within 48 hours, which aligns with current guideline recommendations. Thus, the relative delay in initiation of nutrition observed in this study may not have been long enough to contribute to patient outcomes. Future studies could investigate if delaying enteral nutrition for 48 hours in COVID-19 patients affects patient outcomes. In this study, patients who initiated enteral nutrition within 24 hours of mechanical ventilation were compared with a later initiation of enteral nutrition. This selection of the 24-hour cutoff may be controversial. The current recommendation in COVID-19 patients is to initiate enteral nutrition within 12 hours of starting mechanical ventilation. In the experience of the authors, the 12-hour threshold can be challenging to meet in the setting of surge staffing, and the significance of a 24-hour threshold was thus studied instead.

Patients who received enteral nutrition within 24 hours did receive a greater amount of weight-based calories and protein per day. However, the provision of both was still well below goal requirements, and absolute differences in

TABLE 2. Nutrition Provision.

Characteristics	n = 155
Daily calories, kcal/kg IBW, mean (SD)	16.1 (5.5)
Daily protein, g/kg IBW, mean (SD)	0.93 (0.38)
Time to starting enteral nutrition, d, median (IQR)	1.16 (0.52)
Started enteral nutrition within 24 h, n (%)	60 (38.7)
Started enteral nutrition within 48 h, n (%)	108 (69.7)
Received enteral nutrition while on vasopressor, n (%)	116 (74.8)
Developed hyperglycemia, n (%)	122 (78.7)
Days with hyperglycemia, mean (SD)	3.86 (2.69)
Developed hypoglycemia, n (%)	18 (11.6)
Developed severe hypophosphatemia, n (%)	24 (15.5)
Enteral tube location	
Gastric only, n (%)	140 (93.5)
Postpyloric only, n (%)	2 (1.4)
Both gastric and postpyloric, n (%)	2 (1.4)
Unclear, n (%)	6 (3.9)
Received prokinetic medication, n (%)	10 (6.5)
Received multivitamin, n (%)	19 (12.3)
Enteral nutrition formula	
Nutren 1.5, n (%)	118 (76.1)
Nutren 2.0, n (%)	8 (5.2)
Novasource renal, n (%)	62 (40)
Replete, n (%)	2 (1.3)
Nepro, n (%)	2 (1.3)

IBW, ideal body weight; IQR, interquartile range.

daily calorie and protein provision were small. These small differences may, in part, explain why early nutrition did not impact outcomes. However, similar outcomes were observed when patients were compared with those who received a daily calorie provision of at least 15 kcal/kg. The Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults (PERMIT) trial compared permissive underfeeding to standard feeding in critically ill adults. Patients in the permissive underfeeding arm received 46% of goal calories compared with 71% in the standard-care arm, with no differences in outcomes observed.[23] The Initial Trophic vs Full Enteral Feeding in Patients with Aute Lung Injury (EDEN) trial compared initial trophic with full enteral feeding in patients with ALI and found that a greater calorie provision did not increase the number of ventilator-free days or reduce mortality.[13] Early parenteral nutrition in patients with contraindications to enteral nutrition has also been examined in a randomized control trial. Patients receiving early parenteral nutrition received more calories and protein per day, yet no differences mortality, length of stay, or complications were observed.[11]

Aggressive nutrition has also been shown to potentially harm outcomes in patients with ALI. The Intensive Nutriton in Acute Lung Injury (INTACT) trial compared early intensive nutrition therapy with standard nutrition therapy. Patients in the intensive nutrition therapy arm received significantly more calories and protein. Mortality was 40% in the intensive nutrition group compared with 15.8% in the standard nutrition therapy group, a significant difference.[14] In the current study, there was no signal that early initiation of enteral nutrition or greater calorie provision was harmful in COVID-19 patients. Early nutrition could result in more hyperglycemia, which has been demonstrated to increase incidence of nosocomial complications.[24,25] However, patients who received nutrition within 24 hours of mechanical ventilation did not experience more days of hyperglycemia after propensity score analysis was incorporated.

To the knowledge of the authors, this is one of the first reports describing nutrition support for COVID-19 patients in the United States. The results of this study have implications for the care of critically ill COVID-19 patients. Despite a high severity of illness, it was still possible to deliver enteral nutrition to these patients often within 48 hours of being intubated. The presence of gastrointestinal symptoms on admission did not appear to limit the ability to provide enteral nutrition once mechanically ventilated in this cohort. However, the severity of these gastrointestinal symptoms is unclear, given the retrospective nature of this study. Over 70% of patients received enteral nutrition despite also

TABLE 3. Patient Outcomes.

Outcome	n = 155
Inpatient mortality, n (%)	42 (27.1)
Inpatient length of stay, median (IQR)	22.0 (23.8)
ICU length of stay, median (IQR)	14.3 (14.4)
Days alive and ventilator free at 60 d, mean (SD)	32.5 (21.3)
Required tracheostomy, n (%)	26 (16.8)
Readmission to ICU following ICU discharge, n (%)	7 (4.5)
Discharge on new oxygen requirement	41 (26.5)
Discharge location	
Home, n (%)	62 (40)
Rehab facility, n (%)	26 (16.7)
Skilled nursing facility, n (%)	21 (13.6)
Long-term acute care hospital, n (%)	1 (0.6)
Still admitted to hospital, n (%)	4 (2.6)
Deceased, n (%)	42 (27.1)

ICU, intensive care unit; IQR, interquartile range; Rehab, rehabilitation.

receiving vasopressor medications. This practice was associated with an excellent safety profile, as no patients developed bowel ischemia that required intervention. Although greater calorie provision was not associated with improved outcomes in this study, very few patients received 100% of goal calories. Previous trials have demonstrated that it is very challenging to provide 100% of goal calories with conventional enteral nutrition strategies alone.[12,13] Volume-based enteral nutrition strategies or supplemental parenteral nutrition may be necessary to provide 100% of caloric goals in this patient population. More research is necessary to clarify the role of parenteral nutrition in patients with COVID-19. An ongoing prospective, observational trial examining caloric needs in mechanically ventilated COVID-19 patients, using indirect calorimetry, should provide more information.[26]

This study does have several limitations. Nutrition assessment was limited by an inability to examine patients and perform nutrition-focused physical assessments. Oral intake prior to admission was likewise often unclear. It is possible that many patients, after several days of experiencing COVID-19, presented with poor oral intake and that they were already at a significant calorie deficit prior to the initiation of mechanical ventilation. A supplemental multivitamin was not routinely administered to patients during the first 7 days of mechanical ventilation. Owing to the retrospective nature of this project and documentation inconsistencies, gastric residual volumes, vomiting, and the decision to stop enteral nutrition on the basis of gastric residual volumes could not be assessed. Glucose control was challenging in these patients. Insulin infusions were generally avoided because of the need to frequently enter patient rooms to check glucose levels and adjust infusion rates. Overall incidence of hyperglycemia in these patients was nevertheless higher than ideal. Because of the risk of infection spread and surge staffing, daily calorie counts were not recorded for patients that were extubated and eating. This study is subject to the limitations inherent to retrospective evaluations (bias, confounding variables, etc). However, we attempted to minimize the impact of these limitations through the use of propensity score matching. Following propensity score matching, differences in calorie and protein provision still existed despite no apparent differences in severity of illness. These differences in enteral nutrition provision could be attributed to heterogeneity in practice among different providers. However, other undetermined variables that were not collected may have contributed to nutrition provision as well.

The natural history of COVID-19 infections and the complexity of presentation is not yet well understood. Nutrition intake may only play a small role in survival for the most critically ill patients with COVID-19 pneumonia. The results of this study suggest that initiation of enteral nutrition within 24 hours of starting mechanical ventilation may not improve outcomes in COVID-19 patients. Additional studies are necessary to further clarify the ideal time to initiate enteral nutrition in critically ill patients with COVID-19.

Statement of Authorship

N. Farina, S. Nordbeck, J. Cherry-Bukowiec, M. D. Kraft, M. R. Pleva, and E. Raymond equally contributed to the conception and design of the research; M. Montgomery, L. Cordwin, and F. Blair contributed to the design of

TABLE 4. Comparison by Initiation Time of Enteral Nutrition (n = 155).

Characteristics	Started within 24 hours of starting mechanical ventilation (n = 60)	Started after 24 hours of starting mechanical ventilation (n = 95)	*P*-value
Age, y, mean (SD)	58.3 (14.1)	61.5 (13.6)	.166
Weight, kg, median (IQR)	100 (33.3)	96 (36)	.481
BMI (median)	33.2 (12.8)	33.2 (11.2)	.530
APACHE II, mean (SD)	23.4 (6.4)	26.8 (7.5)	.005
SOFA, mean (SD)	9.0 (2.8)	10.4 (3.1)	.006
NUTRIC ≥ 5, n (%)	38 (63.3)	75 (78.9)	.042
PaO_2/FiO_2 ratio, median (IQR)	142 (81.5)	118 (83)	.594
Neuromuscular blockade, n (%)	19 (31.7)	29 (30.5)	1.00
Inhaled nitric oxide, n (%)	10 (16.7)	10 (10.5)	.327
Prone positioning, n (%)	15 (25)	26 (27.4)	.852
ECMO, n (%)	3 (5)	3 (3.2)	.677
Tocilizumab, n (%)	25 (41.7)	45 (47.4)	.512
Daily calories, kcal/kg/d, mean (SD)	17.5 (4.7)	15.2 (5.8)	.015
Daily protein, g/kg/d, mean (SD)	1.04 (0.34)	0.85 (0.39)	.003
Time to starting enteral nutrition, d, median (IQR)	0.65 (0.47)	1.99 (2.43)	.006
Inpatient length of stay, d, median (IQR)	18.5 (24.4)	23.5 (21.5)	.37
Mortality, n (%)	17 (28.3)	25 (26.3)	.842
ICU length of stay, d, median (IQR)	12.9 (10.1)	14.7 (17.9)	.07
Days alive and ventilator free at 60, mean (SD)	31.3 (22.3)	33.3 (20.7)	.743
Tracheostomy, n (%)	7 (11.7)	19 (20)	.194
Discharge to home, n (%)	24 (40)	38 (40)	1.00
Days of hyperglycemia, mean (SD)	4.4 (2.6)	3.5 (2.7)	.048
Hypoglycemia, n (%)	8 (13.3)	10 (10.5)	.615
Severe hypophosphatemia, n (%)	14 (23.3)	10 (10.5)	.04

APACHE, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NUTRIC, Nutrition Risk in Critically Ill; PaO_2, partial pressure of oxygen; SOFA, Sequential Organ Failure Assessment.

the research; N. Farina, S. Nordbeck, M. Montgomery, L. Cordwin, and F. Blair contributed to the acquisition and analysis the of data; N. Farina, S. Nordbeck, M. Montgomery, L. Cordwin, F. Blair, J. Cherry-Bukowiec, M. D. Kraft, M. R. Pleva, and E. Raymond contributed to the interpretation of the data; and N. Farina drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

TABLE 5. Propensity-Matched Comparison by Start of Enteral Nutrition Within 24 Hours (n = 100).

Characteristics	Started within 24 hours (n = 50)	Started after 24 hours (n = 50)	*P*-value
Age, y, mean (SD)	58.9 (14.1)	59.6 (13.8)	.544
Weight, kg, median (IQR)	100 (36.2)	95.8 (37.5)	.341
BMI (median)	34.5 (13.8)	33.3 (8.7)	.424
APACHE II, mean (SD)	23.5 (6.4)	25.3 (6.0)	.160
SOFA, mean (SD)	9.4 (2.9)	1.0 (2.6)	.232
NUTRIC ≥ 5, n (%)	31 (62)	36 (72)	.395
PaO_2/FiO_2 ratio, median (IQR)	141 (75.9)	132 (88.8)	.758
Neuromuscular blockade, n (%)	18 (36)	17 (34)	1.00
Inhaled nitric oxide, n (%)	8 (16)	4 (8)	.357
Prone positioning, n (%)	11 (22)	13 (26)	.815
ECMO, n (%)	2 (4)	2 (4)	1.00
Tocilizumab, n (%)	22 (44)	24 (48)	.841
Daily calories, kcal/kg/d, mean (SD)	17.7 (4.6)	15.1 (5.1)	.009
Daily protein, g/kg/d, mean (SD)	1.03 (0.35)	0.86 (0.38)	.014
Time to starting enteral nutrition, d, median (IQR)	0.65 (0.47)	1.97 (2.68)	<.001
Inpatient length of stay, d, median (IQR)	18.5 (25.0)	24.6 (20.6)	.136
Mortality, n (%)	14 (28)	11 (22)	.644
ICU length of stay, d, median (IQR)	13.0 (11.4)	15 (18.6)	.389
Days alive and ventilator free at 60, mean (SD)	31.4 (22.4)	35.3 (20.0)	.36
Tracheostomy, n (%)	6 (12)	11 (22)	.287
Discharge to home, n (%)	20 (40)	25 (50)	.422
Days of hyperglycemia, mean (SD)	4.3 (2.5)	3.5 (2.7)	.129
Hypoglycemia, n (%)	5 (10)	4 (8)	1.00
Severe hypophosphatemia, n (%)	12 (24)	6 (12)	.192

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NUTRIC, Nutrition Risk in Critically Ill; PaO_2, partial pressure of oxygen; SOFA, Sequential Organ Failure Assessment.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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