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Relation between nutrition therapy in the acute phase and outcomes of ventilated patients with COVID-19 infection: a multicenter prospective observational study

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ABSTRACT

Background: Optimal nutrition therapy has not yet been established for the acute phase of severe coronavirus disease 2019 (COVID-19) infection.

Objectives: We aimed to examine the effects of nutrition delivery in the acute phase on mortality and the long-term outcomes of post-intensive care syndrome (PICS).

Methods: A multicenter prospective study was conducted on adult patients with COVID-19 infection requiring mechanical ventilation during an intensive care unit (ICU) stay. Daily total energy (kcal/kg) and protein (g/kg) deliveries in the first week of the ICU stay were calculated. The questionnaire for PICS evaluation was mailed within a median of 6 mo after hospital discharge. The primary outcome was in-hospital mortality, and secondary outcomes were the PICS components of physical impairment, cognitive dysfunction, and mental illness.

Results: Among 414 eligible patients, 297 who received mechanical ventilation for 7 d or longer were examined. PICS was evaluated in 175 patients among them. High protein delivery on days 4–7 correlated with a low in-hospital mortality rate. In contrast, high protein delivery on days 1–3 correlated with physical impairment. A multivariate logistic regression analysis adjusted for age, sex, BMI, and severity revealed that average energy and protein deliveries on days 4–7 correlated with decreased in-hospital mortality (OR: 0.94; 95% CI: 0.89, 0.99; P = 0.013 and OR: 0.40; 95% CI: 0.17, 0.93; P = 0.031, respectively). Nutrition delivery did not correlate with PICS outcomes after adjustments. In the multivariate regression using a restricted cubic spline model, in-hospital mortality monotonically decreased with increases in average nutrition delivery on days 4–7.

Conclusions: In patients with COVID-19 on mechanical ventilation for ≥7 d, nutrition delivery in the late period of the acute phase was monotonically associated with a decrease in in-hospital mortality. Adequate protein delivery is needed on days 4–7. This trial was registered at https://www.umin.ac.jp as UMIN000041276.

Keywords: PICS, post-intensive care syndrome, ICU-AW, intensive care unit acquired weakness, COVID-19, nutrition, protein, energy

Introduction

Nutrition therapy is one of the important components of critical care. Although adequate nutrition is crucial for the maintenance of life, the immune system, and body composition, permissive underfeeding with 70%–80% of the estimated energy expenditure is suggested in the early period of the acute phase (1, 2). The optimal intake of protein is more controversial. Although the secure provision of protein is considered to be crucial (3–5), amino acid loads induce damage by impairing autophagy in the early period of the acute phase (6). Although some guidelines recommend 1.2–2.0 g·kg⁻¹·d⁻¹ (7) or 1.3 g·kg⁻¹·d⁻¹ (1) protein, there is currently no information on the optimal timing to achieve these targets in the acute phase.

In the recent coronavirus disease 2019 (COVID-19) pandemic, the number of critically ill patients who require mechanical ventilation in the intensive care unit (ICU) has been increasing (8). Hyperinflammation and prolonged mechanical ventilation...
may lead to muscle volume losses (9) and a number of functional disabilities, which is known as post-intensive care syndrome (PICS) (10). Urgent statements from societies recommend the administration of similar nutrition therapy to patients with COVID-19 infection as that to critically ill patients in order to prevent PICS (11, 12). Optimal nutrition therapy has not yet been established for the acute phase of COVID-19; however, it may be examined in more detail than in other critical diseases owing to the relatively homogeneous population with a single organ dysfunction of the lungs and tolerance for enteral nutrition (13).

Therefore, we conducted a multicenter prospective study to investigate the outcomes of adult patients with COVID-19 infection who required mechanical ventilation, and its relation with nutrition delivery in the first 7 d in the ICU. To examine whether energy and protein deliveries in the early and late periods (1) had different effects on outcomes and if their timings for targets to be achieved were around the transition period, we analyzed energy and protein deliveries in the first 3 d and days 4–7 within the first 7 d in the ICU and their relations with outcomes in patients requiring mechanical ventilation for 7 d and longer.

Methods

This was a multicenter prospective study that investigated the long-term outcomes of severe COVID-19 infection, named the PICS-COVID study (Post-Intensive Care outcomeS in patients with CoRonaVirus Disease 2019). Thirty-two ICUs in Japan participated in the present study, which was approved by the Institutional Review Board of the National Hospital Organization Tokyo Medical Center (date: 26 November, 2020; approval number: R20-133) and the review board of each participating hospital. The study protocol was registered in the University Hospital Medical Information Network (UMIN000041276). The present study was performed in line with the principles of the Declaration of Helsinki.

Adult patients with COVID-19 who required mechanical ventilation during an ICU stay and were discharged from the ICU between March 2020 and December 2020 were included. Patients who were unable to walk independently before hospitalization, regardless of the use of assistive devices, were excluded from the analysis. COVID-19 infection was laboratory-confirmed using a real-time PCR. Written informed consent was obtained from all patients in the analysis, including regarding the publication of their data, and patients who died in hospitals were registered if there was no indication of opt-out.

Clinical data included basic characteristics [age; sex; height; body weight; BMI (in kg/m²)]; Sequential Organ Failure Assessment (SOFA) scores at the start of ventilation; age, dehydration, respiratory failure, orientation disturbance, and blood pressure (A-DROP) scores on ICU admission; clinical frailty scale scores; and comorbidities], treatments [tracheostomy, the administration of corticosteroids, the maximum daily dose of a prednisolone equivalent (0 mg/d if no corticosteroids were used), the continuous administration of neuromuscular-blocking drugs, prone positioning, extracorporeal membrane oxygenation, and renal replacement therapy], in-hospital outcomes (in-hospital death, lengths of ICU and hospital stays, and the duration of mechanical ventilation), and nutrition therapy.

The nutrition protocol was not defined in the present study, and nutrition provision was decided by each attending physician in the participating facility. In general and frequent practices in Japan, energy of 20 kcal · kg⁻¹ · d⁻¹ and protein of 1 g · kg⁻¹ · d⁻¹ are the targets within the first 7 d of the acute phase, with more energy and protein being achieved after the acute phase (14). Indirect calorimetry was not used. In total, 17 of 32 (53.2%) facilities used their own nutrition protocols, whereas the others did not. Daily total energy (kcal) and protein (g) deliveries in the first week of the ICU stay were calculated by physicians. Enteral nutrition and parenteral nutrition were registered separately. Regarding parenteral nutrition, calories of products with energy concentrations ≤5% of glucose solution and propofol calories were not included in calculations. In cases in which oral intake had already begun, the amount estimated from actual intake was recorded. After ICU discharge, energy and protein deliveries were not tracked. There were no missing values in nutrition delivery during the ICU period.

The questionnaire for PICS evaluation after hospital discharge was mailed to patients in February 2021. It consisted of simple questions regarding physical function, cognitive function, and mental health. Physical and cognitive functions and mental health status compared with those before ICU admission were reported as a patient self-reported score on a 10-point visual analog scale, with a higher score indicating a better condition. The Barthel index (BI) (15) was used to assess physical function; the Short-Memory Questionnaire (SMQ) (16) for cognitive function; the Hospital Anxiety and Depression Scale (HADS) (17) for mental health, anxiety, and depression; and the EuroQol 5 Dimension 5 Level (EQ-5D-5L) (18) for quality of life (QOL). Patients were asked to answer the questionnaire by themselves or with a family member or acquaintance. The patients who answered the questionnaire were incentivized with a gift voucher of 10 USD.

In-hospital mortality was the primary outcome of the present study. Secondary outcomes were the outcomes evaluated in the questionnaire, particularly PICS physical impairment. We defined PICS as the occurrence of any physical, cognitive, or psychiatric impairment (10). Physical impairment was defined as <90 points on the BI (19), cognitive impairment as <40 points on the SMQ (20), and mental impairment as >8 points on HADS-anxiety or depression (21). A decline in QOL was defined as <0.8 points on the EQ-5D-5L (22).
We divided patients into 2 groups, one in which the duration of mechanical ventilation was <7 d and another in which it was 7 d or longer. Because BMI ≥25 is defined as obesity in Asian countries (23), energy and protein deliveries were calculated as kcal·kg⁻¹·d⁻¹ and g·kg⁻¹·d⁻¹, respectively, using actual body weight in patients with BMI <40 and adjusted body weight (ideal body weight as BMI 25 + actual body weight/3) in patients with BMI ≥40 (2). The average of each nutrition delivery in the ICU on days 1–3 and 4–7 was calculated. The baseline characteristics and outcomes were compared between groups divided according to their median. We also assessed the relations between each nutrition delivery as a continuous variable and the primary/secondary outcomes with univariable and multivariable regression analyses adjusted for age, sex, BMI, and SOFA scores.

Statistical analysis

After examining the distribution of data by the Shapiro–Wilk test, continuous variables were expressed as means ± SDs and compared using Student’s t test, or expressed as medians [IQRs] and compared using the Mann–Whitney U test. Categorical variables were expressed as n (%) and compared using the chi-square test. When missing values were noted in a patient’s questionnaire responses, the nominal scale was analyzed as 0, and continuous variables were excluded from the analysis. A multivariable logistic regression analysis of in-hospital mortality, PICS physical impairment, cognitive impairment, and mental illness was performed with adjustments for age, sex, BMI, and SOFA scores, which were not regarded as multicollinear factors, in order to investigate the relations between energy or protein delivery and these outcomes. We also performed a multivariable logistic regression analysis of in-hospital mortality and PICS physical impairment with adjustments for age, sex, BMI, SOFA scores, individual facilities, and evaluation times, as well as a sensitivity analysis using nutrition delivery of 1–2 and 3–7 d as comparison groups.

Moreover, to assess nonlinear associations between the average energy/protein delivery on days 4–7 and each outcome, we fitted restricted cubic spline models in the multivariate logistic regression analysis. Restricted cubic splines are a way of evaluating the nonlinear relation between a predictor and an outcome. The range of values of the predictor is subdivided using a set of knots, and the regression curves between each set of knots join smoothly at the knot. The probabilities with 95% CIs of in-hospital mortality and each PICS aspect estimated from the value of the average energy/protein delivery on days 4–7 were evaluated in restricted cubic spline models with 4 knots. A post hoc power analysis was conducted for in-hospital mortality with nutrition deliveries divided according to the median value in each period. Spline curves were analyzed using R version 4 (Toukei Kagaku Kenkyujo, Co., Ltd, Japan); all statistical analyses were conducted using JMP 14 software (SAS Institute Inc.). Results with a P value < 0.05 were inferred as indicating a significant difference.

Results

Figure 1 shows the study outline. Between March 2020 and December 2020, 566 patients were treated with mechanical ventilation in the participating ICUs; of these, 414 eligible patients were registered in the study. Each facility registered a median [IQR] of 7 [4–16] patients. Among the 337 patients who survived and were discharged from the hospital, 251 answered the questionnaire for PICS evaluation. A total of 297 patients were on mechanical ventilation for ≥7 d. Among these patients, 70 died
in the hospital, 227 were discharged, and 175 were evaluated for PICS outcomes. The median [IQR] duration from ICU discharge to the PICS evaluation was 6 mo [3–9 mo]. None of the patients had missing clinical information. Supplemental Table 1 lists the number of missing values for the PICS questionnaire.

Table 1 shows the baseline characteristics, treatments, nutrition therapy, and outcomes in patients with mechanical ventilation < 7 d and ≥ 7 d. SOFA scores were higher and most outcomes were worse in patients with mechanical ventilation ≥ 7 d. Regarding nutrition therapy, daily average energy (kcal) and protein (g) deliveries as median values were 5.8 kcal · kg⁻¹ · d⁻¹ and 0.3 g · kg⁻¹ · d⁻¹ on days 1–3 and 14.3 kcal · kg⁻¹ · d⁻¹ and 0.7 g · kg⁻¹ · d⁻¹ on days 4–7, respectively. Energy was mostly delivered by enteral nutrition on days 1–3 and 4–7 irrespective of the duration of mechanical ventilation. Supplemental Figure 1 describes in detail the energy and protein deliveries on each day. Supplemental Table 2 shows characteristics of patients for whom PICS could not be assessed (n = 86).

Table 2 shows major outcomes in patients with mechanical ventilation ≥ 7 d by dividing the sample according to the median value of each nutrition delivery in each period (as aforementioned). As a primary outcome, in-hospital mortality was significantly lower in the higher protein group on days 4–7: 28.9% for days 4–7 protein < 0.7 g · kg⁻¹ · d⁻¹ and 18.2% for days 4–7 protein ≥ 0.7 g · kg⁻¹ · d⁻¹ (P = 0.031). Similar results were not observed for energy delivery on days 4–7 or nutrition delivery on days 1–3. In the post hoc analysis, power (1−β) for in-hospital mortality was 0.289 in days 1–3 energy, 0.593 in days 4–7 energy, 0.953 in days 1–3 protein, 0.947 in days 4–7 energy, and 0.999 in days 4–7 protein. In contrast, regarding PICS outcomes as a secondary outcome, the rate of PICS physical impairment was significantly higher in the higher protein group on days 1–3: 15.6% for days 1–3 protein < 0.3 g · kg⁻¹ · d⁻¹ and 32.9% for days 1–3 protein ≥ 0.3 g · kg⁻¹ · d⁻¹ (P = 0.0078). Higher energy delivery on days 4–7 was also associated with PICS physical impairment: 15.9% for days 4–7 energy < 14 g · kg⁻¹ · d⁻¹ and 30% for days 4–7 energy ≥ 14 g · kg⁻¹ · d⁻¹ (P = 0.027).

### Table 1 Overall information

|                  | Mechanical ventilation < 7 d | Mechanical ventilation ≥ 7 d | P value |
|------------------|------------------------------|------------------------------|---------|
| n                | 117                          | 297                          |         |
| Age, y           | 67.5 ± 11.4                  | 66.9 ± 12.5                  | 0.62    |
| Male             | 91 (77.8)                    | 239 (80.5)                   | 0.54    |
| BMI, kg/m²       | 25.2 ± 4.3                   | 25.9 ± 5.1                   | 0.19    |
| SOFA score on the day of starting ventilation | 5 [3.5–7] | 6 [4–8] | 0.012 |
| A-DROP on ICU admission | 2 [1–3] | 2 [1–3] | 0.86    |
| Clinical frailty scale before hospitalization | 2 [1–3] | 2 [1–3] | 0.77    |
| Comorbidities:   |                              |                              |         |
| Hypertension     | 51 (43.6)                    | 133 (44.8)                   | 0.83    |
| Diabetes         | 31 (26.5)                    | 117 (39.4)                   | 0.012   |
| Cardiac diseases | 18 (15.4)                    | 39 (13.1)                    | 0.55    |
| End-stage renal disease | 2 (1.7) | 10 (3.4) | 0.34    |
| Autoimmune diseases | 3 (2.6) | 13 (4.4) | 0.37    |
| Malignant tumors | 9 (7.7)                      | 22 (7.4)                     | 0.92    |
| Chronic obstructive pulmonary disease | 8 (6.8) | 34 (11.5) | 0.15    |
| Immunodeficiency | 3 (2.6)                      | 14 (4.7)                     | 0.30    |
| Treatment received during hospital stay |                       |                              |         |
| ECMO             | 1 (0.9)                      | 60 (20.2)                    | <0.0001 |
| Tracheostomy     | 2 (1.7)                      | 79 (26.6)                    | <0.0001 |
| Maximum prednisolone dose, mg/d | 41.25 [30–77.5] | 44 [20–100] | 0.25    |
| Continuous neuromuscular blocking agent | 55 (47.0) | 129 (43.4) | 0.51    |
| Prone position   | 46 (39.3)                    | 150 (50.5)                   | 0.039   |
| Renal replacement therapy | 3 (2.6) | 49 (16.5) | <0.0001 |
| Nutrition therapy provision |                       |                              |         |
| Days 1–3 energy (average), kcal · kg⁻¹ · d⁻¹ | 4.97 [3.12–7.78] | 5.80 [3.61–9.44] | 0.032   |
| Days 1–3 protein (average), g · kg⁻¹ · d⁻¹ | 0.28 [0.12–0.44] | 0.30 [0.15–0.49] | 0.25    |
| Days 1–3 EN calorie/total calorie, % | 100 [100–100] | 100 [100–100] | 0.33    |
| Days 4–7 energy (average), kcal · kg⁻¹ · d⁻¹ | 10.7 [7.36–16.4] | 14.3 [9.41–18.58] | <0.0001 |
| Days 4–7 protein (average), g · kg⁻¹ · d⁻¹ | 0.56 [0.26–0.85] | 0.70 [0.41–0.93] | 0.013   |
| Days 4–7 EN calorie/total calorie, % | 100 [85.3–100] | 100 [100–100] | 0.20    |
| In-hospital mortality | 7 (6.0) | 70 (23.6) | <0.0001 |
| Length of ICU stay, d | 7 [5–8] | 15 [11–26] | <0.0001 |
| Length of hospital stay, d | 9 [7–20] | 27 [17–45.75] | <0.0001 |
| Duration of mechanical ventilation, d | 5 [4–6] | 13 [9–23] | <0.0001 |

1Values are means ± SDs compared using Student’s t test or medians [IQRs] compared using the Mann–Whitney U test for continuous variables; values are n (%) compared using the chi-square test for categorical variables. P values < 0.05 indicate a significant difference. A-DROP, age, dehydration, respiratory failure, orientation disturbance, and blood pressure; ECMO, extracorporeal membrane oxygenation; EN, enteral nutrition; ICU, intensive care unit; SOFA, sequential organ failure assessment.
TABLE 2  
Outcomes of patients on mechanical ventilation for ≥7d

| Outcome                          | Days 1–3 | Days 1–3 | Days 4–7 | Days 4–7 |
|----------------------------------|----------|----------|----------|----------|
| Energy provision (average)       | 38.2 (39) | 36.4 (37) | 36.8 (38) | 37.9 (39) |
| Protein provision (average)      | 1.2 (1.2) | 1.2 (1.2) | 1.2 (1.2) | 1.2 (1.2) |
| Body weight calculation          | 150 (15) | 148 (14) | 149 (15) | 150 (15) |
| In-hospital mortality (n, %)     | 38 (25.0) | 32 (22.1) | 31 (21.2) | 39 (25.8) |
| QOL decline (n, %)               | 36 (41.4) | 39 (45.4) | 34 (37.5) | 42 (49.4) |

Values are n (%), for categorical variables and compared using the chi-square test. Values < 0.05 indicate a significant difference. PICS, post-intensive care syndrome; QOL, quality of life.

Discussion

In patients with COVID-19 on mechanical ventilation for ≥7 d, nutrition delivery on days 4–7 was significantly associated with decreased in-hospital mortality after adjustment, but not with PICS outcomes. In the restricted cubic spline model, in-hospital mortality monotonically decreased with increases in nutrition delivery on days 4–7.

This is the first large-scale study that we know of to investigate the relation between nutrition delivery and the long-term outcomes of severe COVID-19 patients. To the best of our knowledge, limited information is currently available on the dose-dependent influence of nutrition delivery in the early and late periods of the acute phase. Total energy and protein deliveries were lower than the doses recommended in international guidelines (1, 7). Under these conditions, lower nutrition delivery in the late periods of the acute phase was associated with a higher mortality rate. The European Society for Clinical Nutrition and Metabolism proposed the concept of days 1–2 being the early period and days 3–7 being the late period in the acute phase, and suggested a strategy to change nutrition therapy at these transition periods (1). We divided the acute phase into days 1–3 and days 4–7; specifically, we included day 3 in the early period because nutrition delivery often reached its target pace during day 3 (2). The present results suggest that transition of the nutrition strategy in the acute phase should be made on either of ICU days 3 or 4. In seriously ill patients who required ≥7 d of mechanical ventilation, systemic inflammatory response syndrome and a compensated anti-inflammatory syndrome peak occurred within the first few days (24), during which overfeeding needs to be avoided. A previous study reported that the energy debt increased too much when nutrition delivery was not adequate.
TABLE 3  Univariable and multivariable logistic regression analyses of in-hospital mortality and PICS physical impairment for patients on mechanical ventilation for \( \geq 7 \) d

| Nutrition therapy provision | In-hospital mortality | PICS physical impairment | In-hospital mortality | PICS physical impairment |
|-----------------------------|-----------------------|--------------------------|-----------------------|--------------------------|
|                             | Unadjusted            | Adjusted by age, sex, BMI, and SOFA score | Unadjusted            | Adjusted by age, sex, BMI, and SOFA score |
| Days 1–3 energy (average), kcal \( \cdot \) kg\(^{-1}\) \cdot d\(^{-1}\) | 0.97 (0.92, 1.03) | 1.07 (0.99, 1.16) | 0.082 | 0.94 (0.87, 1.00) | 0.052 | 1.00 (0.91, 1.09) | 0.93 |
| Days 1–3 protein (average), g \( \cdot \) kg\(^{-1}\) \cdot d\(^{-1}\) | 3.52 (1.23, 10.0) | 0.019 | 13.9 (2.30, 84.5) | 0.0035 | 1.95 (0.58, 6.52) | 0.28 | 3.40 (0.44, 26.3) | 0.24 |
| Days 4–7 energy (average), kcal \( \cdot \) kg\(^{-1}\) \cdot d\(^{-1}\) | 0.96 (0.92, 1.00) | 0.058 | 1.07 (1.01, 1.13) | 0.014 | 0.94 (0.89, 0.99) | 0.013 | 1.03 (0.96, 1.10) | 0.42 |
| Days 4–7 protein (average), g \( \cdot \) kg\(^{-1}\) \cdot d\(^{-1}\) | 0.48 (0.23, 0.99) | 0.042 | 3.08 (1.26, 7.56) | 0.013 | 0.40 (0.17, 0.93) | 0.031 | 1.73 (0.60, 4.97) | 0.31 |

\(^1\)A multivariable logistic regression analysis of in-hospital mortality and PICS physical impairment was performed with/without adjustments for age, sex, BMI, and SOFA score. \( P \) values < 0.05 indicate a significant difference. PICS, post-intensive care syndrome; SOFA, sequential organ failure assessment.

A lack of nutrition in the late period of the acute phase may be a prominent disadvantage via energy debt in targeted patients who require longer ventilation. Therefore, we may need to increase nutrition delivery from that period. Similar results were not obtained in patients on mechanical ventilation for \(< 7 \) d, which may be attributed to extubation overlapping in this period, discharge from the ICU and nutrition not being registered, and voluntary energy intake being affected by appetite loss.

Protein delivery needs to be secured for critical care nutrition as previously reported (26–28). Increased protein delivery might monotonically contribute to lower mortality, based on our results. However, it currently remains unclear whether much more increased energy and protein deliveries affect mortality because nutrition delivery in the present study was relatively low. Larger amounts of protein may be needed and effective for body composition and the immune system with underfeeding in healthy individuals (29), chronic illnesses (30), and acute illnesses (5). In contrast, the adverse effects of protein may be more prominent in the early acute phase. Because this result was consistent with previous findings (31, 32), marked changes in nutrition delivery may be needed at the transition of the early and late periods in the acute phase, particularly for protein delivery.

In the present study, nutrition delivery did not contribute to PICS outcomes, and some factors of nutrition delivery may affect physical impairment. However, few studies have demonstrated that nutrition therapy directly improves the activities of daily living (ADL) or that overfeeding may worsen ICU-acquired weakness (6), as demonstrated in the present study. Early mobilization and rehabilitation may not be possible in facilities worldwide, particularly for COVID-19 infections (33), and nutrition therapy alone may not improve ADL. Further studies are needed to examine the effects of the combination of nutrition therapy and rehabilitation on PICS outcomes.

The present study had several limitations. We need to consider a number of biases because this was an observational study design. Because the present study included all eligible patients admitted to each facility in the study period, we did not calculate the sample size. Furthermore, we were unable to evaluate the degree of pulmonary or neurological damage. Only patients with the ability to walk unassisted were selected; however, some patients may have had comorbid mental disorders. Moreover, the time taken to assess PICS differs between patients. The reliability of some of the questionnaire for PICS evaluation was not confirmed in patients with COVID-19. Regarding nutrition

**FIGURE 2** Nonlinear restricted cubic spline curves of relations between in-hospital mortality (A) and PICS physical impairment (B), and average energy/protein delivery on days 4–7. (A) Estimated in-hospital mortality (\( n=297 \)) and (B) estimated probability of PICS physical impairment (\( n=175 \)) adjusted by age, sex, BMI, and SOFA scores and represented with 95% CIs. PICS, post-intensive care syndrome; SOFA, sequential organ failure assessment.
therapy, nutrition in each hospital was not prescribed or uniform. Nutrition delivery was relatively low in all patients. Therefore, this relation needs to be examined with greater energy and protein deliveries. Although many obese patients were included because of COVID-19 severity risks, their BMI may still have been slightly lower than those in European countries. We calculated nutrition delivery with an adjusted body weight, but did not perform indirect calorimetry to assess precise energy expenditure. Nutrition delivery was only evaluated until ICU day 7. In addition, we did not analyze malabsorption, such as diarrhea, during the ICU stay. Another limitation is that we did not identify the cause of death or whether it correlated with nutrition therapy.

In conclusion, in patients with COVID-19 on mechanical ventilation for ≥7 d, nutrition delivery on days 4–7 was monotonically associated with decreased in-hospital mortality, whereas that on days 1–3 was not. Adequate nutrition, including protein delivery, may be required from the late period of the acute phase rather than from the early period.

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Data Availability

Data described in the article, code book, and analytic code will be made available upon request pending application and approval. Individual participant data that underlie the results reported in the present study are available from the corresponding author upon reasonable request.

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