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Title

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

Short title

Nutrition therapy for COVID-19 ventilated patients

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Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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Abbreviation list:

ADL; activities of daily living, A-DROP; Age, dehydration, respiratory failure, orientation disturbance and blood pressure, BI; Barthel index, BMI; body mass index, COVID-19; coronavirus disease 2019, EQ-5D; EuroQol 5 dimension, HADS; Hospital Anxiety and Depression Scale, ICU; intensive care unit, PICS; post-intensive care syndrome, QOL;

quality of life, SOFA; Sequential Organ Failure Assessment, SMQ; Short-Memory Questionnaire

Abstract

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

OBJECTIVE: To examine the effects of nutrition delivery in the acute phase on the mortality and 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 the PICS evaluation was mailed within a median of 6 months after hospital discharge. The primary outcome was in-hospital mortality, and secondary outcomes were PICS components of physical, cognitive dysfunction and mental illness.

RESULTS: Among 414 eligible patients, 297 who received mechanical ventilation for 7 days 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, body mass index, and severity revealed that average energy and protein deliveries on days 4-7 correlated with decreased in-hospital mortality; odds ratio 0.94 (95%CI 0.89,0.99) ($p=0.013$) and 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 restricted cubic spline model, in-hospital mortality monotonically decreased with increases in average nutrition delivery on days 4-7.

CONCLUSIONS: In patents with COVID-19 on mechanical ventilation ≥7 days, 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.

Keywords: PICS; ICU-AW; COVID-19; nutrition; protein; energy

Introduction

Nutrition therapy is one of the important components of critical care. While 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/day [7] or 1.3 g/kg/day [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 ICU has been increasing [8]. Hyper-inflammation 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 due to the relatively homogenous 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 relationship with nutrition delivery in the first 7 days in ICU. To examine whether energy and protein deliveries in the early and late periods [1] had different effects on outcomes and if their timing for targets to be achieved were around the transition period, we analyzed energy and protein deliveries in the first 3 days and days 4-7 within the first 7 days in ICU and their relationships with outcomes in patients requiring mechanical ventilation for 7 days and longer.

Materials and Methods

This was a multicenter prospective study that investigated the long-term outcomes of severe COVID-19 infection, named Post-Intensive Care outcomeS in patients with COronaVIrus Disease 2019 (The PICS-COVID study). Thirty-two ICU in Japan participated in the present study, which was approved by the Institutional Review Board of the National Hospital Organization Tokyo Medical Center (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).

Adult patients with COVID-19 who required mechanical ventilation during an ICU stay and were discharged from 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 polymerase chain reaction. Written informed consent was obtained from all patients in the analysis, 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, body mass index [BMI], 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/day 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/day and protein of 1 g/kg/day are the targets within the first 7 days of the acute phase, with more energy and protein being achieved after the acute phase [14]. Indirect calorimetry was not used. In total, 17/32 (53.2%) facilities employed 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, the calories of the 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 the 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 the mental health status compared to those before ICU admission were reported as a patient-self reported score with a 10-point Visual Analogue 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 EuroQol 5 dimension (EQ-5D) [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 US dollar.

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 less than 90 points on the BI [19], cognitive impairment as less than 40 points on the SMQ [20], and mental impairment as more than 8 points on HADS-anxiety or depression [21]. A decline in QOL was defined as less than 0.8 points on EQ-5D-5L [22].

We divided patients into 2 groups, one in which the duration of mechanical ventilation was less than 7 days and another in which it was 7 days or longer. Since BMI ≥25 is defined as obesity in Asian countries [23], energy and protein deliveries were calculated as kcal/kg/day and g/kg/day, 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 ICU on days 1-3 and 4-7 was calculated. The baseline and outcomes were compared between groups divided according to their median. We also assessed the relationship 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 ± standard deviations and compared using the Student's *t*-test, or expressed as medians with interquartile ranges and compared using the Mann–Whitney U test. Categorical variables were expressed as numbers with percentages and compared using the chi-squared test. When missing values were noted in a patient's questionnaire responses, the nominal scale was analyzed as zero, 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, which were not regarded as multicollinear factors, in order to investigate the relationships 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, individual facilities, and evaluation times, as well as a sensitivity analysis using nutrition delivery of 1-2 and 3-7 days as comparison groups.

Besides, to assess a non-linear association 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 non-linear relationship 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% confidence intervals (CI) 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 four knots. A *post-hoc* power analysis was conducted for in-hospital mortality with nutrition deliveries dividing the median value in each period. Spline curves were analyzed using R version 4; all statistical analyses were conducted using JMP 14 software (SAS Institute Inc.). Results with a p value <0.05 were inferred as a significant difference.

Results

The study outline is shown in Figure 1. Between March 2020 and December 2020, 566 patients were treated with mechanical ventilation in the participating ICU, and 414 eligible patients were registered in the study. Each facility registered a median (interquartile range) of 7 (4, 16) patients. Among the 337 patients who survived and were discharged from the hospital, 251 answered the questionnaire for the PICS evaluation. A total of 297 patients were on mechanical ventilation ≥7 days. Among these patients, 70 died in the hospital, 227 were discharged, and 175 were evaluated for PICS outcomes. The median duration from ICU discharge to the PICS evaluation was 6 (3, 9) months. None of the patients had missing clinical information. The number of missing values for the PICS questionnaire is listed in Supplementary Table 1.

Table 1 shows the baseline, treatments, nutrition therapy, and outcomes in patients with mechanical ventilation <7 days and ≥7 days. SOFA scores were higher and most outcomes were worse in patients with mechanical ventilation ≥7 days. Regarding nutrition therapy, daily average energy (kcal) and protein (g) deliveries as median values were 5.8 kcal/kg/day and 0.3 g/kg/day on days 1-3 and 14.3 kcal/kg/day and 0.7 g/kg/day 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. Energy and protein deliveries on each day were described in detail in Supplementary Figure 1. Patient characteristics for whom PICS could not be assessed (n=86) are shown in Supplementary Table 2.

In Table 2, major outcomes in patients with mechanical ventilation ≥7 days were shown by dividing the median value of each nutrition delivery in each period (described above). 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/day and 18.2% for days 4-7 protein ≥ 0.7 g/kg/day, respectively (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 1-3 protein, 0.947 in days 4-7 energy and 0.999 in days 4-7 protein, respectively. In contrast, regarding PICS outcomes as a secondary outcome, the rate of PICS physical impairment was significantly higher in the higher protein delivery on days 1-3 group; 15.6% for days 1-3 protein <0.3 g/kg/day and 32.9% for days 1-3 protein ≥0.3 g/kg/day, respectively (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/day and

30% for days 4-7 energy ≥14 g/kg/day (p=0.027). The baseline according to this division and the other outcomes are shown in Supplementary Tables 3 and 4.

Univariable and multivariate logistic regression analyses of in-hospital mortality and PICS physical impairment were performed (Table 3). After adjustments for age, sex, BMI, and SOFA, energy delivery on days 4-7 and protein delivery on days 4-7 correlated with decreased in-hospital mortality; odds ratio 0.94 (95%CI 0.89,0.99) (p=0.013) and 0.40 (95%CI 0.17,0.93) (p=0.031), respectively. Other deliveries were not associated with in-hospital mortality, and nutrition delivery was not associated with PICS physical impairment after adjustments. As a sensitivity analysis, nutrition delivery was divided into days 1-2 and days 3-7 (Supplementary Table 5) and adjusted by age, sex, BMI, SOFA, individual facilities, and evaluation times for PICS physical (Supplementary Table 6). Similar results were obtained in the multivariate regression analysis.

Spline curves of the relationships between average nutrition delivery on days 4-7 and in-hospital mortality/PICS physical impairment are shown in Figure 2. Estimated in-hospital mortality monotonically decreased with increases in energy or protein delivery. The probability of PICS physical impairment decreased and turned to increase at a certain point with increases in nutrition delivery. Similar spline curves for the probability of PICS cognitive impairment and mental illness are shown in

Supplementary Figure 2.

The results of similar analyses of patients with mechanical ventilation <7 days are shown in Supplementary Tables 7 and 8.

Discussion

In patients with COVID-19 on mechanical ventilation ≥7 days, 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 average nutrition delivery on days 4-7.

This is the first large-scale study to investigate the relationship between nutrition delivery and the long-term outcomes of severe COVID-19 patients. To 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 the 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 since 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 ICU days 3 or 4. In seriously ill patients who required ≥7 days 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 [25]. 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 <7 days, which may be attributed to extubation overlapping in this period, discharge from 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 from 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. Since 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. Since 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 the PICS evaluation was not confirmed in patients with COVID-19. Regarding nutrition therapy, nutrition in each hospital was not prescribed or uniform. Nutrition delivery was relatively low in all patients. Therefore, this relationship 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.

Conclusions

In patients with COVID-19 on mechanical ventilation ≥7 days, nutrition delivery on days 4-7 was monotonically associated with decreased in-hospital mortality, while 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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Declarations

Conflicts of interest

Some authors report potential conflicts of interest outside of this study. Drs. Hatakeyama and Nakamura report lecture fees from Nestle, and Dr. Liu reports personal fees from MERA and receives a salary from TXP Medical completely outside of this study. The other authors have disclosed that they do not have any potential conflicts of interest.

Availability of data and materials

Individual participant data that underlie the results reported in the present study are available from the corresponding author upon reasonable request.

Code availability

Not applicable

Author contributions

JH, NK, and LK contributed to the concept and design of the study. All authors participated in data collection. JH and KN analyzed the data. JH and KN wrote the first draft with input from KY, LK, TN, SI, SO, SH, and ON. All authors contributed to and approved the final manuscript.

Ethics approval

The present study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the National Hospital Organization Tokyo Medical Center (Date: November 26, 2020, Approval number: R20-133)

Consent to participate

Written informed consent was obtained from each patient or their legal representative.

Consent for publication

Patients signed informed consent regarding the publication of their data.

Study registration

The present study is registered in the University Hospital Medical Information Network (UMIN000041276).

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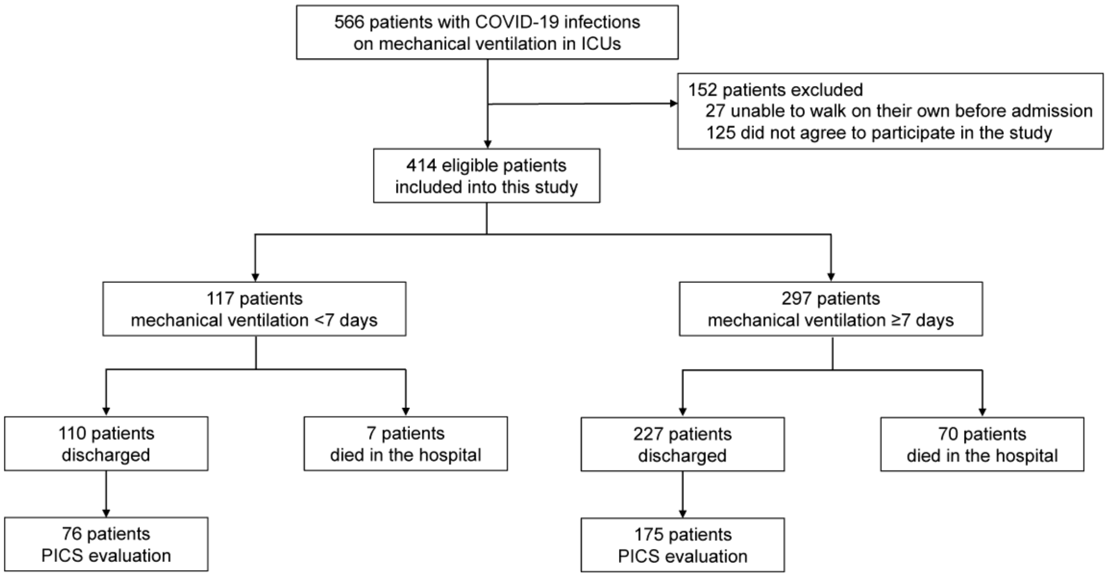

Figure 1 Study outline.

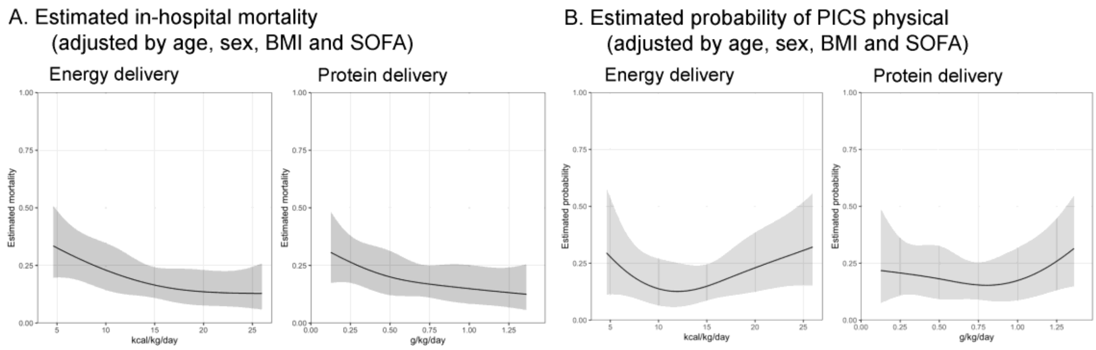

Figure 2 Non-linear restricted cubic spline curves of relationships between in-hospital mortality and PICS physical impairment, and average energy/protein delivery on days 4-7.

The relationships between in-hospital mortality and PICS physical impairment, and average energy/protein deliveries on days 4-7 were shown with a restricted cubic spline model. Estimated in-hospital mortality and the estimated probability of PICS physical impairment were represented with 95%CI. A: Estimated in-hospital mortality adjusted by age, sex, BMI, and SOFA (n=297), B: Estimated probability for PICS physical impairment adjusted by age, sex, BMI, and SOFA (n=175).

PICS: post-intensive care syndrome, BMI: body mass index, SOFA: sequential organ failure assessment score.

Table 1 Overall information

n	Mechanical ventilation <7 days 117	Mechanical ventilation ≥7 days 297	p value
Age, yr	67.5±11.4	66.9±12.5	0.62
Male, n (%)	91 (77.8)	239 (80.5)	0.54
BMI, kg/m^2	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, n (%)	1 (0.9)	60 (20.2)	<0.0001
Tracheostomy, n (%)	2 (1.7)	79 (26.6)	<0.0001
Maximum prednisolone dose, mg/day	41.25 (30, 77.5)	44 (20,100)	0.25
Continuous neuromuscular blocking agent, n (%)	55 (47.0)	129 (43.4)	0.51
Prone position, n (%)	46 (39.3)	150 (50.5)	0.039
Renal replacement therapy, n (%)	3 (2.6)	49 (16.5)	<0.0001

Nutrition therapy provision			
days 1-3 energy (average) (kcal/kg/day)	4.97 (3.12, 7.78)	5.80 (3.61, 9.44)	0.032
days 1-3 protein (average) (g/kg/day)	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/day)	10.7 (7.36, 16.4)	14.3 (9.41, 18.58)	<0.0001
days 4-7 protein (average) (g/kg/day)	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)	0.020
In-hospital mortality (%)	7 (6.0)	70 (23.6)	<0.0001
Length of ICU stay, day	7 (5, 8)	15 (11, 26)	<0.0001
Length of hospital stay, day	9 (7, 20)	27 (17, 45.75)	<0.0001
Duration of mechanical ventilation, day	5 (4, 6)	13 (9, 23)	<0.0001

Continuous variables were expressed as means ± standard deviations and compared using the Student's t-test, or expressed as medians with interquartile ranges and compared using the Mann–Whitney U test. Categorical variables were expressed as numbers with percentages and compared using the chi-squared test. P values <0.05 indicate a significant difference.

A-DROP: Age, dehydration, respiratory failure, orientation disturbance and blood pressure, BMI: Body mass index, SOFA: sequential organ failure assessment score, ECMO: extracorporeal membrane oxygenation, EN: enteral nutrition

Table 2 Outcomes of patients on mechanical ventilation ≥7 days

	Mechanical ventilation ≥ 7 days												
	days 1-3 energy provision (average)			days 1-3 protein provision (average)			days 4-7 energy provision (average)			days 4-7 protein provision (average)			
Adjusted body weight calculation	<6 kcal/kg/day	≥6 kcal/kg/day	p value	<0.3 g/kg/day	≥0.3 g/kg/day	p value	<14 kcal/kg/day	≥14 kcal/kg/day	p value	<0.7 g/kg/day	≥0.7 g/kg/day	p value
n	152	145		146	151		142	155		149	148	
In-hospital mortality (%)	38 (25.0)	32 (22.1)	0.55	31 (21.2)	39 (25.8)	0.35	39 (27.5)	31 (20.0)	0.13	43 (28.9)	27 (18.2)	0.031
PICS %	53 (60.9)	57 (64.8)	0.60	57 (58.2)	53 (68.8)	0.15	49 (58.3)	61 (67.0)	0.23	54 (60.7)	56 (65.1)	0.54
PICS-Physical %	18.6	27.9	0.15	15.6	32.9	0.0078	15.9	30	0.027	18.4	28.2	0.13
PICS-Cognitive %	51.7	50.6	0.88	45.4	58.7	0.083	50.6	51.7	0.89	50.0	52.4	0.75
PICS-mental %	33.3	43.7	0.16	34.7	43.4	0.24	35.7	41.1	0.47	33.0	44.2	0.13
QOL decline, n (%)	36 (41.4)	39 (45.4)	0.60	38 (38.8)	37 (49.3)	0.17	33 (39.3)	42 (47/2)	0.29	33 (37.5)	42 (49.4)	0.11

Categorical variables were expressed as numbers with percentages and compared using the chi-squared test. P values <0.05 indicate a significant difference. PICS: post-intensive care syndrome, QOL: quality of life, HADS: Hospital Anxiety and Depression Scale, EQ5D: EuroQol 5 dimension

Table 3 Univariable and multivariable regression analyses of in-hospital mortality and PICS physical.

	Mechanical ventilation ≥7 days							
	Unadjusted				Adjusted by age, sex, BMI, SOFA			
	In-hospital mortality		PICS physical		In-hospital mortality		PICS physical	
	Odds, 95% CI	p	Odds, 95% CI	p	Odds, 95% CI	p	Odds, 95% CI	p
Nutrition therapy provision								
days 1-3 energy (average), kcal/kg/day	0.97 (0.92,1.03)	0.38	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/kg/day	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/kg/day	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/kg/day	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

A multivariable logistic regression analysis of in-hospital mortality, PICS physical impairment was performed with/without adjustments for age, sex, BMI, and SOFA. The odds ratio (95% confidence interval) was shown. P values <0.05 indicate a significant difference.

PICS: post-intensive care syndrome, BMI: body mass index, SOFA: sequential organ failure assessment score, CI: confidence interval