Relationship between critical care nutrition and post-intensive care syndrome in surviving ventilated patients with COVID-19: a multicenter prospective observational study

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The impact of nutrition therapy in the acute phase on post-intensive care syndrome (PICS) remains unclear. We conducted a multicenter prospective study on adult patients with COVID-19 who required mechanical ventilation for more than three days. The questionnaire was mailed after discharge. Physical PICS, defined as less than 90 points on the Barthel index (BI), was assigned as the primary outcome. We examined the types of nutrition therapy in the first week that affected PICS components. 269 eligible patients were evaluated 10 months after discharge. Supplemental parenteral nutrition (SPN) >400 kcal/day correlated with a lower occurrence of physical PICS (10% vs 21.92%, *p* = 0.042), whereas the amounts of energy and protein provided, early enteral nutrition, and a gradual increase in nutrition delivery did not, and none correlated with cognitive or mental PICS. A multivariable regression analysis revealed that SPN had an independent impact on physical PICS (odds ratio 0.33, 95% CI 0.12–0.92, *p* = 0.034), even after adjustments for age, sex, body mass index and severity. Protein provision ≥1.2 g/kg/day was associated with a lower occurrence of physical PICS (odds ratio 0.42, 95% CI 0.16–1.08, *p* = 0.071). In conclusion, SPN in the acute phase had a positive impact on physical PICS for ventilated patients with COVID-19.

***Key Words*: PICS, ICU-AW, COVID-19, protein, parenteral nutrition**

The long-term sequelae of physical impairments, mental illness, and cognitive dysfunction is called post-intensive care syndrome (PICS), which markedly reduces the quality of life (QOL) of intensive care unit (ICU) survivors.(1) To prevent or reduce PICS, a number of treatments and care strategies, such as ABCDEF bundles, are provided from the acute phase of critical care.(2) One of the important aims of critical care nutrition in patients with PICS is the preservation of physical function and muscle volume.(3) However, nutrition therapy in the acute phase is more complex than and differs from the muscle training programs for healthy individuals because invasion and under-feeding are essential in critical illnesses.(4,5) Furthermore, limited information is currently available on the relationship between critical care nutrition and PICS outcomes.(6)

Critical care nutrition comprises various components. The amounts of energy and protein provided, nutrition delivery via enteral nutrition (EN) or parenteral nutrition (PN), the implementation of early EN and supplemental PN (SPN), and strategies to achieve gradual increases in nutrition delivery need to be considered when determining the type of nutrition therapy in the acute phase, generally considered to be the first 7 days.(7,8) The types and delivery routes of critical care nutrition that are effective against PICS warrant further study.

The sequelae of coronavirus disease 2019 (COVID-19) is a social issue called long COVID.(9,10) Previous studies reported

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that long-term PICS may occur in patients with severe COVID-19 infection.[11–13] Similar to COVID-19 infection, the relationship between critical care nutrition and PICS remains unclear; therefore, we conducted a prospective investigation called the PICS-COVID study to follow-up mechanically ventilated COVID-19 patients.[13] The findings obtained showed that the amounts of energy and protein provided correlated with mortality, but not with half-year PICS.[14] We herein investigated the outcomes of mechanically ventilated COVID-19 patients approximately one year after discharge as well as the relationship between nutrition therapy in the acute phase and one-year PICS. We examined the effects of different types of critical care nutrition on PICS outcomes, with a focus on physical impairments.

Materials and Methods

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), was conducted.[14] Thirty-two ICU in Japan participated in this 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).

In the present study, the one-year outcomes of PICS in adult patients with COVID-19 who required mechanical ventilation during an ICU stay and were discharged from ICU between March 2020 and February 2021 were evaluated using questionnaires. 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.

The questionnaire for the PICS evaluation was mailed to patients approximately one year after ICU discharge between August and October 2021. Comparisons of physical and cognitive functions and the mental health status to those before ICU admission were reported by patients as a self-reported score using a 10-point visual analogue scale (VAS), with a higher score indicating a better condition. The Barthel index (BI) was used to assess physical function,[15] the Short-Memory Questionnaire (SMQ) for cognitive function,[16] the Hospital Anxiety and Depression Scale (HADS) for mental health,[17] anxiety, and depression, and EuroQol 5 dimension (EQ-5D) for QOL.[18] Patients were asked to answer the questionnaire by themselves or with a family member or acquaintance. Patients who answered the questionnaire were incentivized with a gift voucher equivalent 10 US dollars.

Physical PICS, defined as less than 90 points on the BI,[19] was assigned as the primary outcome of the present study. Secondary outcomes were outcomes evaluated in the questionnaire, cognitive PICS of less than 40 points on the SMQ,[20] and mental PICS of 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]

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 (lengths of ICU and hospital stays and the duration of mechanical ventilation), and nutrition therapy.

The nutrition protocol was not defined in this study, and nutrition provision was decided by each attending physician in the participating facility. In general practice 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 provided after the acute phase.[23] Indirect calorimetry was not used. Seventeen out of 32 (53.2%) facilities employed their own nutrition protocols, whereas the others did not. The daily deliveries of total energy (kcal) and protein (g) in the first week of the ICU stay were calculated by physicians. EN and PN were registered separately. Regarding PN, the calorie contents 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. Since BMI ≥25 is defined as obesity in Asian countries,[24] energy and protein deliveries were calculated as kcal/kg/day and g/kg/day, respectively, using actual body weight in patients with BMI <25 and ideal body weight as BMI of 25 in patients with BMI ≥25. There were no missing values in nutrition delivery during the ICU period.

In the present study, the types of critical care nutrition were defined as follows: as the amount of energy provided, maximum energy provision ≥20 kcal/kg/day within the first seven days or not; energy provision ≥20 kcal/kg/day, with a similar amount of protein provided, maximum protein provision ≥1.2 g/kg/day within the first seven days or not; protein provision ≥1.2 g/kg/day, as an early EN achievement, the sum of enteral energy delivery within the first two days ≥500 kcal or not; early EN ≤2 days, as a gradual increase in nutrition provided, the maximum energy delivery date ≥4 ICU days AND the sum of energy delivered during 4 to 7 ICU days ≥twice their sum during 1 to 3 ICU days or not; a gradual increase in energy delivery, and as a supplemental PN (SPN) practice, maximum PN energy delivery >400 kcal/day or not; SPN >400 kcal/day. Since we confirmed that EN was provided to most patients in the previous study, we described PN as SPN.

Statistical analysis. After examining the distribution of data by the Shapiro–Wilk test, continuous variables were expressed as means ± SD and compared using the Student's *t* test or were expressed as a median (interquartile range) 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. Univariable and multivariable logistic regression analyses of physical PICS were performed with critical care nutrition types: energy provision ≥20 kcal/kg/day, protein provision ≥1.2 g/kg/day, early EN ≤2 days, gradual increase in energy delivered and SPN >400 kcal/day. A multivariable regression analysis was also conducted with adjustments for age, sex, BMI, and SOFA. There were no multicollinear relationships. All statistical analyses were conducted using JMP 14 software (SAS Institute Inc., Cary, NC). Results with a p value <0.05 were considered significant.

Results

The study outline is shown in Fig. 1. During the study period, 506 patients were treated with mechanical ventilation for more than three days, and 278 eligible patients who were discharged and provided their consent to participate in the study were included. After the exclusion of 2 patients who died after discharge, 3 lost to the follow-up after discharge, and 4 who declined to answer the questionnaire, 269 patients were included in this study. The median duration from ICU discharge to the

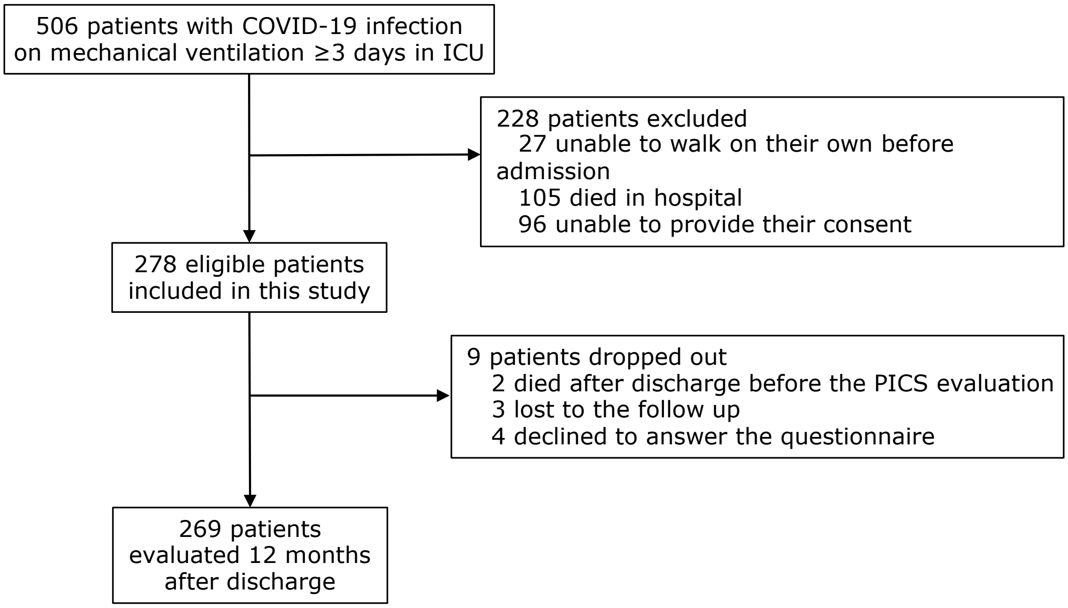

Fig. 1. Study outline. PICS, post-intensive care syndrome.

Table 1. Basic characteristics

n	Overall 269	Physical PICS 50	Non-physical PICS 219	*p* value
Age, years	65.4 ± 11.1	70.7 ± 11.6	64.2 ± 10.7	0.0002
Male, *n* (%)	214 (79.6)	30 (60.0)	184 (84.0)	0.0004
BMI, kg/m^2	25.7 ± 4.2	24.8 ± 4.4	26.0 ± 4.1	0.069
SOFA score on the day of ventilation start	5 (3 7)	5 (4, 7)	5 (3, 7)	0.72
A-DROP on ICU admission	2 (1, 3)	2 (2, 3)	2 (1, 3)	0.024
Clinical frailty scale before hospitalization	2 (1, 2)	2 (1, 2)	2 (1, 3)	0.013
Comorbidities				
Hypertension	132 (49.1)	27 (54.0)	105 (48.0)	0.44
Diabetes	90 (33.3)	18 (36.0)	72 (32.9)	0.67
Cardiac diseases	31 (11.5)	6 (12.0)	25 (11.4)	0.91
End stage renal disease	8 (3.0)	0 (0)	8 (3.7)	0.067
Auto-immune diseases	7 (2.6)	2 (4.0)	5 (2.3)	0.52
Malignant tumors	13 (4.8)	3 (6.0)	10 (4.6)	0.68
Chronic obstructive pulmonary disease	22 (0.08)	7 (14.0)	15 (6.9)	0.12
Immunodeficiency	6 (2.2)	2 (4.0)	4 (1.8)	0.38
Treatment received during hospital stay				
ECMO, *n* (%)	36 (13.4)	5 (10.0)	31 (14.2)	0.42
Tracheostomy, *n* (%)	52 (19.3)	14 (28.0)	38 (17.4)	0.097
Maximum prednisolone dose, mg/day	44 (30, 100)	44 (22.5, 80)	44 (30, 100)	0.91
Continuous neuromuscular blocking agent, *n* (%)	123 (45.7)	21 (42.0)	102 (46.6)	0.56
Prone position, *n* (%)	133 (49.4)	22 (44.0)	111 (50.7)	0.39
Renal replacement therapy, *n* (%)	31 (11.5)	5 (10.0)	26 (11.9)	0.70
Length of ICU stay, day	12 (8, 18.5)	13.5 (8.8, 28.5)	11 (8, 18)	0.14
Length of hospital stay, day	22 (13, 41)	30.5 (18, 53.3)	21 (12, 38)	0.020
Duration of mechanical ventilation, day	9 (6, 16)	11 (6.8, 22.5)	8 (6, 15)	0.021

Continuous variables were expressed as means ± SD and compared using the Student's *t* test or were 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. A-DROP, age, dehydration, respiratory failure, orientation disturbance, and blood pressure; ICU, intensive care unit; BMI, Body mass index; SOFA, sequential organ failure assessment score; ECMO, extracorporeal membrane oxygenation.

PICS evaluation was 10 (9, 14) months. None of the patients had missing clinical information.

The basic characteristics of all patients and those with/without physical PICS are shown in Table 1. The physical PICS group was significantly older and included fewer males. BMI was slightly lower in the physical PICS group. No significant differ-

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Table 2. PICS outcomes

n	Overall 269	Physical PICS 50	Non-physical PICS 219	*p* value
PICS physical components				
Barthel Index	100 (95, 100)	72.5 (63.8, 100)	100 (100, 100)	<0.0001
VAS physical condition	7.0 ± 2.1	5.5 ± 2.7	7.4 ± 1.7	<0.0001
Dyspnea, *n* (%)	126 (47.4)	29 (60.4)	104 (44.5)	0.045
Walking difficulty, *n* (%)	74 (27.8)	30 (60.0)	44 (20.4)	<0.0001
Weight loss, *n* (%)	76 (28.5)	22 (44.0)	54 (24.9)	0.0088
PICS mental components				
PICS-mental, *n* (%)	71 (26.6)	27 (55.1)	44 (20.2)	<0.0001
HADS score	7 (3, 13.)	13 (6, 19)	6 (2, 11.2)	<0.0001
HADS-Anxiety score	3 (1,6)	4 (1, 9)	3 (1, 6)	0.0082
HADS-Depression score	4 (1, 7)	7 (5, 12)	3 (1, 6)	<0.0001
VAS mental health	7.6 ± 2.2	6.1 ± 2.6	7.9 ± 2.0	<0.0001
Depression, *n* (%)	108 (40.3)	26 (52)	82 (37.4)	0.046
Anxiety, *n* (%)	141 (52.4)	34 (68)	107 (48.9)	0.013
Sleeping disorder, *n* (%)	115 (42.8)	30 (60)	85 (38.8)	0.0065
PICS cognitive components				
PICS-Cognitive, *n* (%)	132 (50.2)	36 (72)	96 (44.7)	<0.0001
Short-Memory Questionnaire	39 (35, 43)	35 (24, 39.5)	40 (36, 43)	<0.0001
VAS cognitive function	8.1 ± 1.9	7.1 ± 1.7	8.3 ± 1.7	<0.0001
Memory impairment, *n* (%)	79 (29.5)	20 (40)	59 (26.9)	0.060
Execution disability, *n* (%)	124 (46.6)	32 (64)	92 (42.4)	0.0036
PICS physical components				
Barthel Index	100 (95, 100)	72.5 (63.8, 100)	100 (100, 100)	<0.0001

Categorical variables were expressed as numbers with percentages and compared using the *chi*-squared test. PICS, post-intensive care syndrome; VAS, visual analogue scale; QOL, quality of life; HADS, Hospital Anxiety and Depression Scale; EQ5D, EuroQol 5 dimension.

ences were observed in severity or comorbidities between the two groups, although A-DROP slightly increased with age in the physical PICS group. The length of ICU stays did not significantly differ, whereas the length of hospital stays were 30.5 (18, 53.3) days in the physical PICS group and 21 (12, 38) days in the non-physical PICS group, $p = 0.020$. In addition, the duration of mechanical ventilation was 11 (6.8, 22.5) and 8 (6, 15) days in the physical and non-physical PICS groups, respectively ($p = 0.021$).

Table 2 shows the one-year outcomes of PICS. One-fifth (50/269) of patients had physical PICS. The physical PICS group had not only worse outcomes related to physical impairments, but also to mental illness and cognitive dysfunction, including HADS and SMQ scores. QOL was significantly worse in the physical PICS group; EQ-5D-5L was 0.67 (0.47, 0.85) in the physical PICS group and 0.87 (0.78, 1) in the non-physical PICS group ($p<0.0001$).

Nutrition delivery in the first seven ICU days in patients with/without physical PICS is shown in Fig. 2. Data are shown as medians with interquartile ranges. Nutrition delivery was almost 0 kcal/kg/day in the first day and gradually increased to medians of approximately 15 kcal/kg/day of energy and 0.8 g/kg/day of protein by days four to five in both groups. The proportion of enteral energy delivery was high and most patients received EN. Therefore, PN was described as SPN in the present study. The trajectory of nutrition delivery was similar in the physical PICS and non-physical PICS groups.

The impact of critical care nutrition types, defined as energy provision ≥20 kcal/kg/day, protein provision ≥1.2 g/kg/day, early EN ≤2 days, gradual increases in energy delivery and SPN >400 kcal/day, on the occurrence of physical PICS was analyzed using univariable and multivariable regression analyses (Table 3). In the univariable analysis, only SPN had a significantly negative impact on physical PICS; odds ratio 0.40, 95% confidence interval (CI) 0.15–0.99, $p = 0.042$. The multivariable regression analysis revealed that SPN also had a significantly independent impact from the other types of nutrition therapy; odds ratio 0.33, 95% CI 0.10–0.85, $p = 0.021$. Furthermore, SPN had a significantly negative impact on the occurrence of physical PICS after adjustments for age, sex, BMI, and SOFA scores in the multivariable regression analysis of the other types of nutrition therapy; odds ratio 0.34, 95% CI 0.11–0.99, $p = 0.049$. On the other hand, protein provision ≥1.2 g/kg/day was negatively associated with the occurrence of physical PICS; however, the analysis lacked the power to detect a significant difference; odds ratio 0.42, 95% CI 0.16–1.08, $p = 0.071$.

The provision of SPN in the first seven days is shown in Supplemental Fig. 1*****. While almost no nutrition was provided parenterally in the no-SPN group, nutrition delivery gradually increased by days four to five, similar with the overall total nutrition delivery with medians of approximately 8 kcal/kg/day of energy and 0.3 g/kg/day of protein in the SPN group. Outcome differences with/without SPN are shown in Table 4. SPN was associated with higher BI and VAS physical condition and a lower incidence of weight loss but not with mental illness, cognitive dysfunction, or QOL; however, VAS mental health and VAS cognitive function were significantly higher in the SPN group.

Discussion

In the one-year follow-up of surviving patients with COVID-19 who required mechanical ventilation for more than three days, one-fifth had physical PICS. SPN in the first seven days correlated with a lower occurrence of physical PICS and

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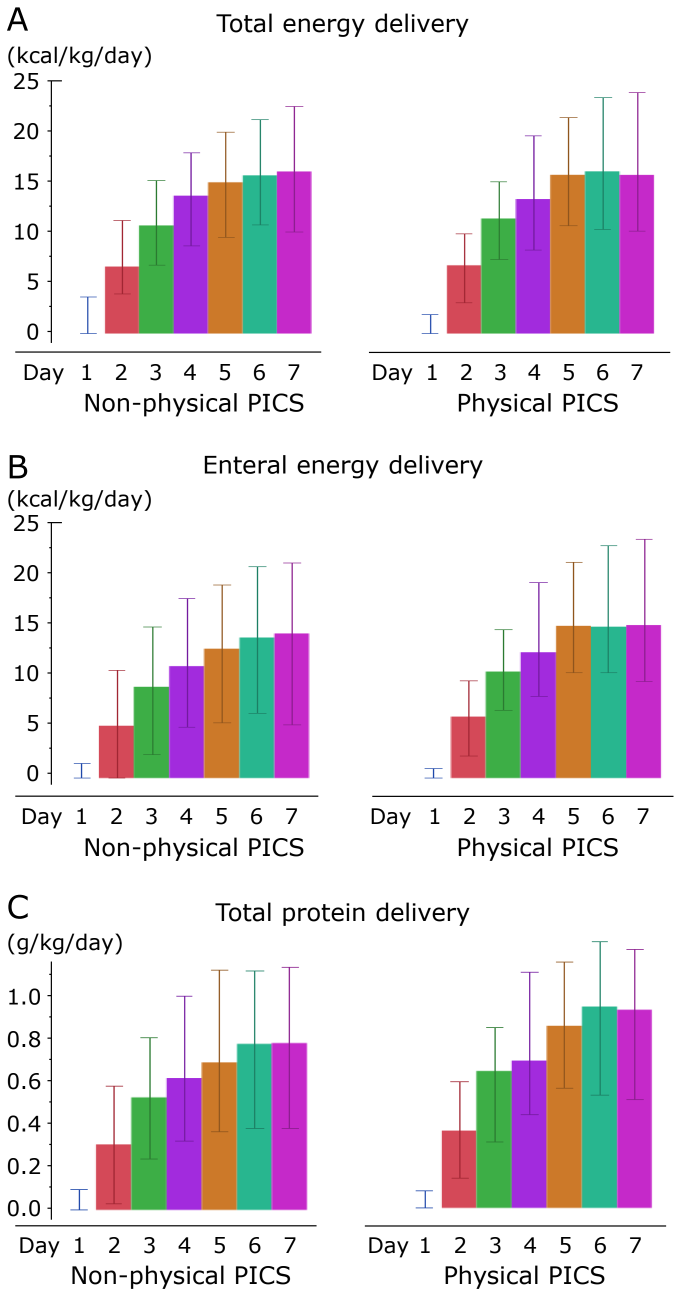

Fig. 2. Nutrition delivery in the first seven days with/without physical PICS. PICS, post-intensive care syndrome.

lower BI and VAS physical condition, while the other types of nutrition therapy did not. The multivariable regression analysis showed that SPN had an independent impact on physical PICS.

Physical PICS was more frequent in both older and female patients, which is consistent with previous findings.[25] A longer duration of mechanical ventilation was associated with physical PICS, whereas severity was not. The duration of mechanical ventilation was previously suggested to be a strong risk factor for physical PICS.[26] Since physical PICS was associated with mental and cognitive PICS, measures against physical PICS are important; however, we did not identify a cause-and-effect relationship.

Although critical care nutrition, particularly nutrition therapy only in the first week may not markedly influence PICS, SPN was associated with the occurrence of physical PICS. The mechanisms by which SPN affected PICS independent of the amounts of nutrition delivered remain unclear; however, direct nutrition delivery via PN might be involved. Since gastrointestinal symptoms have been reported to some extent in patients with COVID-19,[27] nutrients may not be absorbed in the intestinal tract via EN, particularly in patients with diarrhea receiving critical care.[28] Although direct nutrition delivery to systemic organs via PN is occasionally harmful, particularly for the immune system,[29,30] SPN with appropriate amounts of energy after the early acute phase may be beneficial, as demonstrated in a previous RCT.[31] We speculate that nutrition practice with initial underfeeding followed by gradual increases in amounts of SPN may have maximized the effects of SPN in the present study. Furthermore, SPN may have a more significant impact in low nutrition provision practices, which was provided to this study population.

Neither the energy amount nor early EN was confirmed to affect the occurrence of physical PICS in the present study. Nutrition therapy may maintain muscle volume.[3] However, nutrition therapy alone does not affect physical function or the activities of daily living, and its combination with exercise and rehabilitation may be required for it to be effective.[7] The amount of energy delivered was found to be less effective in COVID-19 practices, which restrict early rehabilitation, particularly during the study period. Nevertheless, protein delivery appeared to decrease physical PICS; however, the statistical analysis performed in the present study lacked power. The importance of protein provision for PICS rather than energy provision from the late period of the acute phase has been demonstrated in previous studies and systematic reviews.[6,32–34]

SPN and the other types of nutrition therapy examined did not affect mental or cognitive PICS. Nutrition therapy interventions have recently been proposed for mental illness and cognitive dysfunctions.[35,36] Although difficulties are associated with achieving these aims in critical care nutrition, inappropriate nutrition therapy may negatively impact critical care. The relationship between malnutrition/obesity and mental illness and that between vitamin/trace elements and cognitive dysfunction may be affected by the critical care nutrition practice of underfeeding.[37,38] As a diet management program would be effective for appetite loss as long-term sequelae of COVID-19,[39] such interventions may be able to support PICS including mental and cognitive problems.

The present study had several limitations that need to be addressed. A number of biases need to be considered because this was an observational study. Only patients with the ability to walk unassisted were selected; however, some patients may have had comorbid mental disorders. Furthermore, the time taken to assess PICS differed to some extent between patients. Regarding nutrition therapy, nutrition delivery in each hospital was not prescribed or uniform. Nutrition delivery was low in all patients. Since the calorie contents of parenteral products with energy concentrations ≤5% of glucose solution and propofol calories were not included in calculations, energy delivery may have been underestimated in this study. However, since nutrition delivery was still lower than nutrition practices in European countries,[7] it needs to be examined in future studies with higher energy and protein deliveries. Although many obese patients were included in this study because obesity is a risk factor for COVID-19, 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. Another limitation is that we did not analyze malabsorption, such as diarrhea, during the ICU stay.

SPN with an appropriate dose in the acute phase may affect physical PICS in critical care for ventilated patients with

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Table 3. Univariable and multivariable regression analyses for physical PICS

	Odds, 95% CI	*p*	Multivariable logistic regression analysis			
			Odds, 95% CI	*p*	with age, sex, BMI, and SOFA	
					Odds, 95% CI	*p*
Energy provision ≥20 kcal/kg/day	1.37 (0.74–2.54)	0.31	1.71 (0.75–3.87)	0.20	1.20 (0.50–2.89)	0.69
Protein provision ≥1.2 g/kg/day	0.90 (0.46–1.78)	0.76	0.57 (0.24–1.33)	0.19	0.42 (0.16–1.08)	0.071
Early enteral nutrition ≤2 days	1.04 (0.56–1.93)	0.91	0.73 (0.30–1.75)	0.49	0.88 (0.34–2.29)	0.79
Gradual increase in energy delivery	1.13 (0.59–2.17)	0.72	0.99 (0.43–2.28)	0.98	1.15 (0.47–2.82)	0.76
Supplemental parenteral nutrition >400 kcal/day	0.40 (0.15–0.99)	0.042	0.33 (0.10–0.85)	0.021	0.34 (0.11–0.99)	0.049

A multivariable logistic regression analysis of in-hospital mortality and PICS physical impairment was performed with/without adjustments for age, sex, BMI, and SOFA. The odds ratio (95% confidence interval) was shown. PICS, post-intensive care syndrome; BMI, body mass index; SOFA, sequential organ failure assessment score; CI, confidence interval.

Table 4. PICS outcomes with/without supplemental parenteral nutrition

n	SPN 53	No SPN 216	*p* value
PICS physical components			
PICS-Physical, *n* (%)	5 (9.4)	45 (20.8)	0.042
Barthel Index	100 (100,100)	100 (95, 100)	0.029
VAS physical condition	7.5 ± 1.6	6.9 ± 2.2	0.041
Dyspnea, *n* (%)	22 (41.5)	104 (48.8)	0.34
Walking difficulty, *n* (%)	15 (28.3)	59 (27.7)	0.93
Weight loss, *n* (%)	10 (18.9)	66 (30.8)	0.074
PICS mental components			
PICS-mental, *n* (%)	11 (20.8)	60 (27.5)	0.31
HADS score	6 (2, 12)	7 (3, 13)	0.53
HADS-Anxiety score	3 (1,6)	3 (1, 7)	0.97
HADS-Depression score	3 (1, 6)	4 (1, 7)	0.38
VAS mental health	8.1 ± 1.7	7.5 ± 2.4	0.051
Depression, *n* (%)	22 (41.5)	86 (40.0)	0.84
Anxiety, *n* (%)	28 (52.8)	113 (52.4)	0.95
Sleeping disorder, *n* (%)	20 (37.7)	95 (44.0)	0.41
PICS cognitive components			
PICS-Cognitive, *n* (%)	28 (53.9)	104 (49.3)	0.56
Short-Memory Questionnaire	39 (36, 42)	40 (34, 43)	0.94
VAS cognitive function	8.6 ± 1.4	8.0 ± 2.0	0.031
Memory impairment, *n* (%)	11 (20.8)	68 (31.6)	0.11
Execution disability, *n* (%)	23 (43.4)	101 (47.4)	0.60
Quality of life			
EQ-5D-5L	0.89 (0.77, 1)	0.83 (0.74, 1)	0.26

Categorical variables were expressed as numbers with percentages and compared using the *chi*-squared test. PICS, post-intensive care syndrome; VAS, visual analogue scale; QOL, quality of life; HADS, Hospital Anxiety and Depression Scale; EQ5D, EuroQol 5 dimension.

COVID-19. Protein provision ≥1.2 g/kg/day appeared to be associated with a lower occurrence of physical PICS.

Author Contributions

KN and JH contributed to the concept and design of the study. All authors participated in data collection. KN analyzed the data. KN wrote the first draft and all the authors revised it. All authors contributed to and approved the final manuscript.

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Abbreviations

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

Conflict 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.

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