Original Article

Early enteral nutrition improves the outcome of critically ill patients with COVID-19: A retrospective study

Sheng Wu MD[1], Jian Lou MD[2], Peng Xu MD[3], Rubin Luo MD[3], Libin Li MD[3]

[1]*Department of Neurology, Second Affiliated Hospital of Zhejiang University, Hangzhou, China*
[2]*Department of Respiratory Medicine, Second Affiliated Hospital of Zhejiang University, Hangzhou, China*
[3]*Intensive Care Unit, Second Affiliated Hospital of Zhejiang University, Hangzhou, China*

Background and Objectives: To evaluate the nutritional status of critically ill patients with COVID-19 and to determine which route of nutrition support is advantageous. **Methods and Study Design:** This retrospective study was conducted in the ICU of a designated COVID-19 hospital. Patients were divided into an enteral nutrition (EN) group and parenteral nutrition (PN) group according to the initial route of nutrition support. NRS-2002 and NUTRIC were used to assess nutritional status. Blood nutritional markers such as albumin, total protein and hemoglobin were compared at baseline and seven days later. The primary endpoint was 28-day mortality. **Results:** A total of 27 patients were enrolled in the study - 14 in the EN group and 13 in the PN group - and there were no significant demographic differences between groups. Most patients (96.3% NRS2002 score ≥5, 85.2% NUTRIC score ≥5) were at high nutritional risk. There was no significant difference in baseline albumin, total protein and hemoglobin levels between groups. After 7 days, albumin levels were significantly higher in the EN group than in the PN group (p=0.030). There was no significant difference in the other two indicators. The 28-day mortality was 50% in the EN group and 76.9% in the PN group. Kaplan-Meier survival analysis revealed significant differences between the groups (p=0.030). Cox proportional risk regression indicated that route of nutrition support was also an independent prognostic risk factor. **Conclusions:** The incidence of nutritional risk in critically ill patients with COVID-19 is very high. Early EN may be beneficial to patient outcomes.

Key Words: COVID-19, enteral nutrition, parenteral nutrition, mortality, ICU

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus, SARS-CoV-2, that was first recognized in Wuhan, China, in December 2019. As of September 9, 2020, the total number of patients has risen to 27,688,740 around the world and the death toll has reached 899,315.[1] Whereas most people with COVID-19 develop mild or uncomplicated illness, approximately 14% develop severe disease requiring hospitalization and oxygen support, and 5% require admission to an intensive care unit (ICU).[2]

Nutrition support is well known to play an important role in the treatment of patients with severe respiratory diseases, but data on the nutritional status and nutrition support of critically ill patients with COVID-19 are scarce. Many studies and guidelines have suggested that early (within 24 or 48 hours of admission) enteral nutrition (EN) support can significantly decrease mortality in critically ill patients.[3-6] However, some critically ill patients with COVID-19 require initiation of nutrition support via a parenteral route because of gastrointestinal symptoms or for other medical reasons. In this study, we investigated the nutritional status of critically ill patients with confirmed COVID-19 and retrospectively compared the clinical outcomes of different routes of nutrition support.

METHODS

Patients

This single-center, retrospective study was performed at the ICU of Wuhan Union Hospital Tumor Center (Wuhan, Hubei), a designated COVID-19 hospital. This ICU was taken over by a volunteer medical team dispatched from Second Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, Zhejiang). In accordance with the deployment of the National Health Commission, a total of 29 critically ill patients with COVID-19 were admitted to this ICU from February 15, 2020 to February 29, 2020. All patients with laboratory confirmation of SARS-CoV-2 infection met the criteria for being critically ill. According to the Chinese Clinical Guidance for COVID-19 (7th Edition), criteria of critically ill is as fol-

Corresponding Author: Dr Rubin Luo, Intensive Care Unit, Second Affiliated Hospital of Zhejiang University, 88 Jiefang Rd, Hangzhou 310009, China.
Tel: 86-571-8778 4610
Email: zr_lrb@zju.edu.cn
Manuscript received 06 October 2021. Initial review completed 24 December 2020. Revision accepted 06 April 2020.
doi: 10.6133/apjcn.202106_30(2).0002

lows: 1. respiratory failure requiring mechanical ventilation. 2. shock 3. multiple organ failure needed ICU monitoring. Two Patients who died within 48 hours after admission were excluded. A total of 27 patients were enrolled in the study. The patient enrollment process is shown in Figure 1.

Study group definitions

Patients were divided into two groups according to the route of nutrition support initiated in the first week of staying in the ICU: an EN group and a parenteral nutrition (PN) group.

Data collection

Demographic data Electronic medical records, radiological images and laboratory findings for all enrolled cases were reviewed in detail. We collected data on age, sex, initial symptoms, vital signs, mechanic ventilation strategies and chronic medical histories (such as hypertension, diabetes mellitus, renal dysfunction, hepatic dysfunction, malignancy, stroke, chronic pulmonary disease and surgery history).

Disease severity and comorbidities

The Acute Physiology and Chronic Health Evaluation II (APACHE II) were evaluated on the first day of admission to assess the severity of disease. Pneumonia Severity Index (PSI), which is a widely used and approved scale for assessing the severity of respiratory infectious diseases and predicting prognosis was assessed based on clinical status at admission and laboratory findings. Age-adjusted Charlson Comorbidity Index (ACCI) was used to assess the severity of comorbidities in these patients.

Nutrition data

Baseline body mass index（BMI）were collected as the patient's initial nutritional status. We collected nutrition data including daily energy and protein intake on the seventh day of admission, at which time the nutrition data could reflect the patient's true situation of early nutritional intervention.

Nutrition screening tools

Nutritional Risk Screening 2002 (NRS-2002) and Nutrition Risk in the Critically Ill (NUTRIC) were used to assess nutritional status. These measures effectively reflect the nutritional status of patients, including both current potential undernutrition and disease severity.[7,8] An NRS-2002 score ≥3 indicates potential nutrition risk, whereas a score ≥5 indicates high nutrition risk. Because IL-6 is not routinely measured in our ICU, a NUTRIC score ≥5 suggested high nutritional risk. Laboratory results, such as serum albumin, total protein and hemoglobin were also recorded at baseline and seven days later as markers of nutritional status.

Nutrition support procedures

Nutrition support was delivered within 24 hours after admission. The physician on duty decided which nutritional support route to initiate. Some physicians followed the usual protocol for severe pneumonia and preferred EN if there were no contraindications. Others preferred PN for the following considerations: 1. There would be cough and vomiting in the process of gastric intubation, resulting in aerosol dispersion which would lead to unnecessary occupational exposure. 2. COVID-19 was often accompanied by gastrointestinal symptoms, such as diarrhea, nausea, vomiting and anorexia. Premature EN might aggravate diarrhea and gastroesophageal reflux leading to fluid and electrolyte imbalance and secondary bacterial infection.

In the EN group, patients received first-¬line EN through nasogastric or nasojejunal tubes with a nutrition pump. Two simple formulas were used to estimate daily

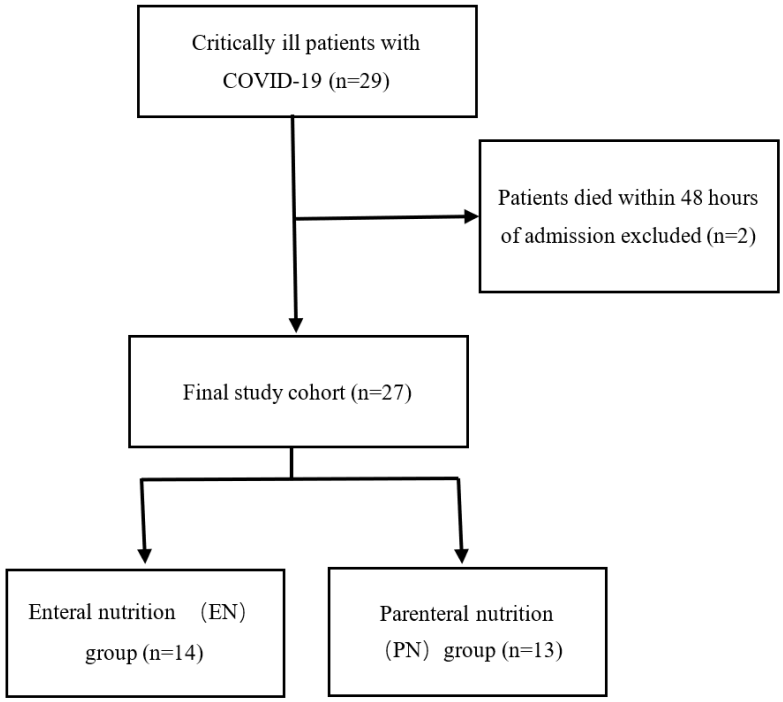

Figure 1. Flow diagram of patient recruitment.

energy and protein requirements: [25–30 kcal/kg/day] *body weight and 1.2 g/kg/day* body weight. In the first week, trophic (10–15 kcal/kg/day) EN was initiated and then patients were gradually transitioned to full-energy EN. Whole-protein preparations with relatively high caloric content were selected (SSPC, China or Nutricia, Netherlands). Patients with intestinal damage received predigested short peptide preparations (SSPC, China), and hyperglycemic patients received nutritional preparations beneficial for glycemic control (SSPC, China). While feeding, patients were seated in a semi-reclining position of 30°–45°. Prokinetic agents and probiotics were used to prevent regurgitation and dysbacteriosis. After 1 week, energy intake and nutrition status were reassessed. If patients were not receiving adequate energy or protein, the nutrition strategies were optimized, such as by adding supplemental PN.

In the PN group, 1 patient who could feed herself received partial parenteral nutrition (PPN) from the peripheral vein. The remaining 12 patients received total parenteral nutrition (TPN) via a central venous catheter for at least 7 days after admission. In the first week, a low-calorie strategy (≤20 kcal/kg/day) was used. A commonly used formula was: Glucose: 50% to 60% of non-protein calories, which was adjusted according to blood glucose. Structural lipid emulsion (Fresenius-Kabi Germany): 250 mL/day. 11.4% Compound amino acids (SPSS China): 250-500 mL/day. Multi-trace elements (Fresenius-Kabi Germany), Fat-soluble and water-soluble vitamins (SPSS China) were also given at the same time. After 1 week, the physician reassessed the nutritional status of the patients, and decided whether to continue TPN, add EN, or switched to EN according to the patient's situation.

Medication and oxygen therapy

All patients were treated in accordance with the principles recommended in the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment. Patients were given antiviral treatment within 24 hours of admission (ribavirin 500 mg 2 times a day + arbidol 200 mg 3 times a day). Antibiotics (quinolones, third generation cephalothins, β -lactamase inhibitor compounds et al, according to the bacterial culture results) were used if the patient had a complicated bacterial infection or if the patient was at high risk of secondary infection. Adequate fluid resuscitation and vasoactive drugs were administered immediately if patients showed signs of circulatory failure. Traditional Chinese medicine (Lianhua Qingwen capsules) were also used according to the patient's condition.

Relief of hypoxemia was the core of our treatment. Patients with the following conditions: SpO_2 <93%; PaO/FiO2 <300 mmHg (1 mmHg = 0.133 kPa); respiratory rate >25 times per min at bed; or remarkable progression on X-ray imaging were immediately given high-flow nasal cannula (HFNC) oxygen therapy or non-invasive ventilation. If there was no relief within 2 hours, tracheal intubation and mechanical ventilation would be performed in time.

Outcomes

The primary outcome was 28-day mortality rate after ICU admission. Secondary outcomes included hemoglobin, serum total protein and serum albumin levels at baseline and seven days after nutrition support.

Data analysis

Demographic information, disease and nutrition therapy related information, laboratory findings and clinical outcomes were recorded and analyzed according to variable type. Continuous variables are reported as mean (standard deviation), and categorical variables are reported as frequency (percentage). Shapiro-Wilk test was used for normality test. Normal distribution data were analyzed using an unpaired Student's t-test between two groups. Non-normal distribution data were analyzed using the Mann-Whitney U test. Categorical variables were compared with chi-squared test or Fisher's exact test. Kaplan–Meier survival curves were used to plot the survival curves of patients. The Cox proportional hazard regression model was used to evaluate potential associations between nutrition group (EN or PN) and 28-day mortality. To assess the impact of confounding factors, we first performed univariate regression analysis to analyze variables that might be associated with mortality rate, such as age, sex, disease duration, APACHE-II score, mechanical ventilation, comorbidities, NUTIRC score, and NRS2002 score. After that, route of nutrition support, age, and APACHE-II score were included as variables in the Cox regression analysis according to clinical experience and statistical results. A p value <0.05 was considered statistically significant. SPSS 25.0 software (IBM Inc., 2010, USA) was used for all analyses.

Ethics

The Ethics Commission of the Second Affiliated Hospital of Zhejiang University approved data collection for this study (Yan 2020–220). Due to the retrospective nature of the study, informed consent was waived.

RESULTS

Baseline characteristics

A total of 27 patients were recruited for this retrospective study, 14 in the EN group and 13 in the PN group. The baseline characteristics of the participants are shown in Table 1 and were similar between groups. The average age was 74.9±10.5 years; 18 (66.7%) were men. 23(85.2%) had chronic underlying diseases, primarily hypertension (14/27), heart disease (10/27), diabetes mellitus (7/27) and chronic obstructive pulmonary disease (7/27), average ACCI score was 4.1±2.0. The median duration from onset of symptoms to ICU admission was 8 days (4–23). The average APACHE II score was 19.2±4.8, average PSI score was 132±15.5. During the first week after admission, a total of 18 (66.7%) patients were treated with mechanical invasive ventilation, 7 (25.9%) patients were treated with non-invasive ventilation, and 2 (7.4%) patients were treated with high flow nasal cannulas for oxygen therapy.

Energy and protein intake

Data of energy and protein intake of patients in the two groups are shown in Table 1. There was no significant difference in BMI between the groups, and there was no

Table 1. Baseline characteristics and nutrition data

	EN group (n=14)	PN group (n=13)	*p* value
Age (years)	72.7±10.2	77.1±10.7	0.296
Gender (male/female)	11/3	7/6	0.236
Respiratory support			0849
invasive ventilation	10	8	
non-invasive ventilation	3	4	
high flow nasal cannulas	1	1	
ACCI	4.2±2.5	4.1±1.4	0.860
APACHE II	19.4±4.8	18.9±5.1	0.792
PSI	132±17.6	132±13.1	0.951
NUTRIC			0.644
<5	2	2	
≥5	12	11	
NRS2002			1.000
<3	0	0	
3,4	1	0	
≥5	13	13	
BMI	23.4±2.0	22.2±2.3	0.161
Energy target (kcal/day)	1603±214	1498±257	0.260
Energy intake (kcal/day)	1400±229	1224±264	0.078
Energy intake/target (%)	87.3±6.7	82.1±14.1	0.241
Protein target (g/day)	77.0±10.3	71.9±12.3	0.260
Protein intake (g/day)	55.6±9.5	37.2±12.7	<0.0001
Protein intake/target (%)	72.9±13.4	51.3±12.7	<0.0001

EN: enteral nutrition; PN: parenteral nutrition; ACCI: Age-adjusted Charlson Comorbidity Index; APACHE II: Acute Physiology and Chronic Health Evaluation II; PSI: Pneumonia Severity Index; NRS-2002: Nutritional Risk Screening–2002; NUTRIC: Nutrition Risk in the Critically Ill; BMI: Body Mass Index..

significant difference in energy or protein requirements according to the simple formulas. In the first week after admission, the daily energy intake of patients in both groups increased gradually. The EN group increased to 1400±229 kcal, reaching 87.3±6.7% of the target (25 kcal/kg/day), and the PN group reached 1224±264kcal, 82.1±14.1% of the target. There was no significant difference between the two groups (p=0.078). However, in terms of daily protein intake, that of EN group (55.6±9.5 g) was much higher than PN group (37.2±12.7g), with significant difference (p<0.001).

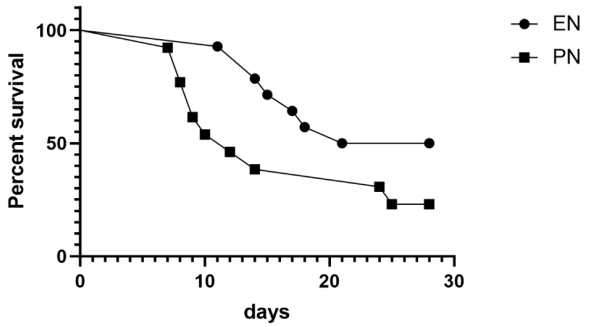

Figure 2. Kaplan–Meier survival curve. Survival curves for EN group vs PN group. Breslow test p=0.030. EN: enteral nutrition group; PN: parenteral nutrition group.

Nutritional markers and mortality

Using two nutritional screening tools, NRS2002 and NUTRIC, we found that the proportion of patients with an NRS2002 score ≥3 was 100% (27/27), and the proportion of patients with an NRS2002 score ≥5 was 96.3% (26/27). The ratio of patients with a NUTRIC score ≥5 was also as high as 85.2% (23/27). The results were similar between groups. At baseline, the mean values of serum albumin, total protein and hemoglobin were 29.4±3.0 g/L, 57.2±2.2 g/L and 107±20.6 g/L in the EN group, respectively, and 29.2±3.2 g/L, 59.3±6.8 g/L and 117±23.9 g/L in the PN group, respectively. There were no significant differences between groups. After one week of treatment, the serum albumin, total protein and hemoglobin in the two groups were re-evaluated, and the mean values were found to be 31.8±4.8 g/L, 63±6.5 g/L and 106±22.1 g/L in the EN group, respectively, and 28.1±5.1 g/L, 60.0±9.7 g/L and 110±21.7 g/L in the PN group, respectively. The serum albumin level was higher in the EN group than the PN group, and there was a significant difference (p=0.030). The other two markers showed no significant difference (Table 2). The overall 28-day mortality for this cohort was 63.0% (17/27). The 28-day mortality of the EN group was 50% (7/14), whereas that of the PN group was 76.9% (10/13). The survival curves of the two groups were represented by a Kaplan-Meier curve (Figure 2), and the Breslow test indicated a significant difference between groups (p=0.030).

Multivariate analysis

In addition to nutrition support modalities, we selected two other factors closely associated with prognosis—age and APACHE II score—on the basis of previous literature.[9] These three factors were used as covariates. Cox proportional hazard regression analysis was performed to identify independent factors associated with prognosis. All three factors were found to be independent risk factors for 28-day mortality (Table 3).

DISCUSSION

Data on nutritional status and nutritional support in critically ill patients with COVID-19 are currently scarce. On the basis of information on other critically ill patients and

Table 2. Nutritional markers at baseline and 7 days later

	EN group (n=14)	PN group (n=13)	*p* value
albumin (g/L)			
Baseline	29.4±3.0	29.2±3.2	0.835
Day 7	31.8±4.8	28.1±5.1	0.030
Total protein (g/L)			
Baseline	57.2±2.2	59.3±6.8	0.267
Day 7	63±6.5	60.0±9.7	0.450
hemoglobin (g/L)			
Baseline	107±20.6	117±23.9	0.261
Day 7	106±22.1	110±21.7	0.671

EN: enteral nutrition; PN: parenteral nutrition

Table 3. Cox proportional hazards regression of 28-day mortality

Independent variable	β	SE	Wald	HR (95% CI)	*p* value
Nutrition support	1.71	0.549	9.64	0.182 (0.062-0.553)	0.002
Age	-0.086	0.041	4.39	0.918 (0.847-0.995)	0.036
APACHE II	0.248	0.080	9.60	1.28 (1.10-1.50)	0.002

SE: standard error; HR: hazard ratio; APACEH II: Acute Physiology and Chronic Health Evaluation II

other respiratory diseases, COVID-19 is expected to pose significant nutritional risks. A meta-analysis has reported that the prevalence of undernutrition risk in pulmonology department inpatients is 36.95%.[10] An international, multicenter, prospective study has reported that the proportion of nutritional risk (NUTRIC ≥5) in critically ill patients admitted to the ICU is 57%.[11] Our study found the incidence of nutritional risk in critically ill patients with COVID-19 to be 85.2%, a proportion much higher than that in previous studies, possibly due to 1. The average age of patients in this cohort was very high. 2. These patients had a very high incidence of comorbidities (80%). 3. According to the APACHE-II and PSI scores, these patients were in a very critical condition. These factors together may have significantly increased their nutritional risk.

The mortality rate in our cohort was higher than that previously reported,[9] possibly because the patients in our cohort were significantly older (age 74.9 vs 59.7), were in more severe condition (APACHE II score 19 vs 17) and had higher ratios of mechanical ventilation (92.6% vs 71%). It is now generally believed that older patients with COVID-19 have significantly higher rates of critical illness and mortality. However, in this cohort, since most of the patients were elderly and the sample size was small, the mortality did not increase with the increase of age. Instead, several very elderly patients (maximum 97 years old) survived.

The importance of nutrition support for the treatment of critically ill patients is well known. Malnutrition may cause infections, muscle wasting, delayed recovery and increased mortality.[12] However, which route of nutrition support should be initiated in critically ill patients remains controversial. A meta-analysis has indicated that the use of EN as opposed to PN may result in an important decrease in the incidence of infectious complications in critically ill patients and may be less costly.[13] Casaer et al have shown that as a supplement to EN, early PN, compared with late PN, not only does not decrease mortality but also increases the risk of ICU infection, mechanical ventilation time and time for renal replacement therapy.[14] However, a randomized, controlled, multicenter open-label, parallel-group study (NUTRIREA-2) has revealed that, compared with PN, isocaloric EN does not reduce mortality or the risk of secondary infections, but is associated with a greater risk of digestive complications.[15] In addition, the CALORIES study has shown that patients with early PN and EN have a similar 30-day mortality.[16] Another study has indicated that EN is associated with a higher overall mortality and a higher incidence of inadequate nutritional intake, complications associated with the delivery system and other feed-related morbidities than PN.[17]

In our study, initiation of EN appeared to be advantageous. According to the literature, we believe these findings may have occurred for the following reasons: 1. PN might impede blood glucose control. Some studies have suggested that hyperglycemia in critically ill patients may lead to an increased risk of infection and poorer outcomes.[18,19] In the early stages of the outbreak, monitoring of blood glucose was not as frequent as usual, to avoid overexposure among medical staff. Therefore, intensive monitoring and tight control of blood glucose could not be achieved at that time. 2. Recently, some studies have identified the gastrointestinal tract as a potential pathway for SARS-CoV-2 infection.[20,21] Some patients have gastrointestinal symptoms such as diarrhea, anorexia and nausea. In contrast, animal model studies and clinical studies have demonstrated that total PN may exacerbate inflammation of the intestinal epithelium and decrease intestinal barrier function, thus leading to bacterial translocation.[22,23] The combination of SARS-CoV-2 infection and PN could lead to an increased risk of infection in patients. 3. Many of these critically ill patients had underlying diseases, particularly diseases affecting the circulatory system, such as cardiac dysfunction, which must be managed strictly through fluid transfusion. PN may aggravate these underlying diseases and cause internal environmental perturbation, thus affecting patient outcomes.

EN also is associated with certain risks.[24] Therefore,

appropriate feeding procedures are crucial. There is little literature on COVID-19 nutrition support. We therefore drew on our experience with other severe respiratory diseases in clinical practice.

First, regarding the time of EN support initiation, it is necessary to initiate EN within 24 hours of admission for hemodynamically stable patients. The results of multiple meta-analyses have shown that early EN, compared with delayed EN, significantly decreases mortality and infection rates. Starting PN within 48 hours is also an appropriate option for patients with hemodynamic instability or the presence of EN contraindications.

Second, many studies have shown that severe underfeeding or overfeeding may increase mortality[25,26] and prolong hospital stay and mechanical ventilation time, and should therefore be avoided as much as possible. However, some recent RCT studies have suggested that full-energy or trophic feeding has no significant effect on patient outcomes.[27,28] We usually initiated trophic (10–15 kcal/h or no more than 500 kcal/day) nutrition support in the first week, because some studies have indicated that starting with trophic nutrition support may decrease the incidence of gastrointestinal intolerance.[29] After a week, we reassessed the nutritional status and energy requirements and then gradually increased the nutrition support or added the other route of nutrition support. Monitoring and tight control of blood glucose should be considered necessary throughout the entire process of nutrition support.

Third, in the process of EN, regular evaluation of gastrointestinal function is required. The acute gastrointestinal injury grading system is usually used to assess the severity.[30] Patient abdominal tension, bowel sounds and defecation, as well as vomiting, aspiration and other conditions, should be observed daily. If feeding intolerance is present, EN must be reduced or suspended.

Fourth, prone position ventilation is an important treatment for critically ill patients with COVID-19. A study has indicated that prone ventilation may result in more gastric retention and higher rates of vomiting and EN termination.[31] However, in our experience, prone ventilation did not significantly increase the adverse effects of EN, but allowed for maintaining an appropriate body position and initiating feeding from a small volume. Some studies have obtained similar findings, in which patients in prone positions tolerated EN well.[32,33]

Conclusions

The incidence of nutritional risk in critically ill patients with COVID-19 is very high and should be taken seriously. In addition, nutrition support should be provided promptly. Early EN (within 24 hours) may be beneficial to patient outcomes. Optimal feeding procedures may prevent the side effects of EN.

Limitations

COVID-19 is an emerging, rapidly evolving pandemic. Our healthcare system was under unprecedented pressure, therefore we were unable to conduct prospective research on nutrition support. Due to the retrospective nature of the study, randomization was not used to allocate patients to EN or PN groups, resulting in an inevitable bias. In this retrospective study, the sample size was small, the follow-up time was short and many clinical indicators could not be obtained. Larger prospective randomized controlled studies are needed to address this issue.

AUTHOR DISCLOSURES

The authors declare that they have no conflict of interest.

REFERENCES

1. World Health Organization. WHO coronavirus disease (COVID-19) Dashboard. 2020/01/21 [cited 2020/09/09]; Available from: https://covid19.who.int/(2020).
2. Wu Z, Mcgoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239-42. doi: 10.1001/jama.2020.2648.
3. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016; 40:159-211. doi: 10.1177/0148607115621863.
4. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. Intensive Care Med. 2009;35:2018-27. doi: 10.1007/s00134-009-1664-4.
5. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264-70. doi: 10.1097/00003246-200112000-00005.
6. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43:380-98. doi: 10.1007/s00134-016-4665-0.
7. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003; 22:321-36. doi: 10.1016/s0261-5614(02)00214-5.
8. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. Crit Care. 2011;15:R268. doi: 10.1186/cc10546.
9. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8:475-81. doi:10.1016/S2213-2600(20)30079-5.
10. Maia I, Peleteiro B, Xará S, Amaral TF. Undernutrition risk and undernutrition in pulmonology department inpatients: a systematic review and meta-analysis. J Am Coll Nutr. 2017; 36:137-47. doi: 10.1080/07315724.2016.1209728.
11. Heyland DK, Dhaliwal R, Wang M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally 'at-risk' critically ill patient: Results of an international, multicenter, prospective study. Clin Nutr. 2015;34:659-66. doi: 10.1016/j.clnu.2014.07.008.
12. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014;370:1227-36. doi: 10.1056/NEJMra1304623.
13. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult

patients? A systematic review of the literature. Nutrition. 2004;20:843-8. doi: 10.1016/j.nut.2004.06.003.
14. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365:506-17. doi: 10.1056/NEJMoa1102662.
15. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133-43. doi: 10.1016/S0140-6736(17)32146-3.
16. Harvey SE, Parrott F, Harrison DA, Sadique MZ, Grieve RD, Canter RR et al. A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). Health Technol Assess. 2016;20:1-144. doi: 10.3310/hta20280.
17. Woodcock NP, Zeigler D, Palmer MD, Buckley P, Mitchell CJ, MacFie J. Enteral versus parenteral nutrition: a pragmatic study. Nutrition. 2001;17:1-12. doi: 10.1016/s0899-9007(00)00576-1.
18. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78:1471-8. doi: 10.4065/78.12.1471.
19. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37:3001-9. doi: 10.1097/CCM.0b013e3181b083f7.
20. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69:997-1001. doi:10.1136/gutjnl-2020-321013.
21. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020;158:1831-3. doi: 10.1053/j.gastro.2020.02.055.
22. Schörghuber M, Fruhwald S. Effects of enteral nutrition on gastrointestinal function in patients who are critically ill. Lancet Gastroenterol Hepatol. 2018;3:281-7. doi: 10.1016/S2468-1253(18)30036-0.
23. Barrett M, Demehri FR, Teitelbaum DH. Intestine, immunity, and parenteral nutrition in an era of preferred enteral feeding. Curr Opin Clin Nutr Metab Care. 2015;18:496-500. doi: 10.1097/MCO.0000000000000208.
24. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med. 1999;27:1447-53. doi: 10.1097/00003246-199908000-00006.
25. Braunschweig CA, Sheean PM, Peterson SJ, Gomez Perez S, Freels S, Lateef O et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). JPEN J Parenter Enteral Nutr. 2015;39:13-20. doi: 10.1177/0148607114528541.
26. Weijs PJ, Looijaard WG, Beishuizen A, Girbes AR, Oudemans-van Straaten HM. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care, 2014;18:701. doi: 10.1186/s13054-014-0701-z.
27. Allingstrup MJ, Kondrup J, Wiis J, Claudius C, Pedersen UG, Hein-Rasmussen R et al. Early goal-directed nutrition versus standard of care in adult intensive care patients: the single-centre, randomised, outcome assessor-blinded EAT-ICU trial. Intensive Care Med. 2017;43:1637-47. doi: 10.1007/s00134-017-4880-3.
28. Arabi YM, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G et al. Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med. 2015;372:2398-408. doi: 10.1056/NEJMoa1502826.
29. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med. 2011;39:967-74. doi: 10.1097/CCM.0b013e31820a905a.
30. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, Braun JP, Poeze M, Spies C. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012; 38:384-94. doi: 10.1007/s00134-011-2459-y.
31. Reignier J, Thenoz-Jost N, Fiancette M, Legendre E, Lebert C, Bontemps F, Clementi E, Martin-Lefevre L. Early enteral nutrition in mechanically ventilated patients in the prone position. Crit Care Med. 2004;32:94-9. doi: 10.1097/01.CCM.0000104208.23542.A8.
32. Saez De La Fuente I, Saez De La Fuente J, Quintana Estelles MD, Garcia Gigorro R, Terceros Almanza LJ, Sanchez Izquierdo JA, Montejo Gonzalez JC. Enteral nutrition in patients receiving mechanical ventilation in a prone position. JPEN J Parenter Enteral Nutr. 2016;40:250-5. doi: 10.1177/0148607114553232.
33. Van Der Voort PH, Zandstra DF. Enteral feeding in the critically ill: comparison between the supine and prone positions: a prospective crossover study in mechanically ventilated patients. Crit Care. 2001;5:216-20. doi: 10.1186/cc1026.