Original Article

Nutritional practice in critically ill COVID-19 patients: A multicenter ambidirectional cohort study in Wuhan and Jingzhou

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Background and Objectives: The novel coronavirus disease (COVID-19) epidemic is spreading all over the world. With the number of cases increasing rapidly, the epidemiological data on the nutritional practice is scarce. In this study, we aim to describe the clinical characteristics and nutritional practice in a cohort of critically ill COVID-19 patients. **Methods and Study Design:** This is a multicenter, ambidirectional cohort study conducted at 11 hospitals in Hubei Province, China. All eligible critical COVID-19 patients in the study hospital intensive care units at 00:00, March 6th, 2020, were included. Data collection was performed via written case report forms. **Results:** A total of 44 patients were identified and enrolled, of whom eight died during the 28-day outcome follow-up period. The median interval between hospital admission and the study day was 24 (interquartile range, 13-26) days and 52.2% (23 of 44) of patients were on invasive mechanical ventilation. The median nutrition risk in critically ill (mNUTRIC) score was 3 (interquartile range, 2-5) on the study day. During the enrolment day, 68.2% (30 of 44) of patients received enteral nutrition (EN), while 6.8% (3 of 44) received parenteral nutrition (PN) alone. Nausea and aspiration were uncommon, with a prevalence of 11.4% (5 of 44) and 6.8% (3 of 44), respectively. As for energy delivery, 69.7% (23 of 33) of patients receiving EN and/or PN were achieving their prescribed targets. **Conclusions:** The study showed that EN was frequently applied in critical COVID-19 patients. Energy delivery may be suboptimal in this study requiring more attention.

Key Words: enteral nutrition, coronavirus, feeding, target-reaching rate, supplemental parenteral nutrition

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INTRODUCTION

Critical cases account for approximately five to seven percent of all the patients with COVID-19, according to the largest reports in and outside the original epicenter, Wuhan[1] and the majority of these patients require intensive care unit (ICU) admission. Yang et al showed that the median length of ICU stay could be as long as eight days.[2] Another study conducted in Washington state also demonstrated long-term ICU stay in a group of 21 patients with critical COVID-19, stressing the importance of appropriate nutritional practice.[3]

Nutritional support is of great importance in intensive care as it may improve ICU outcomes and also alter post-hospital recovery of survivors, especially for patients who require prolonged ICU care.[4] The onset of malnutrition is common in critically ill patients and is associated with increased morbidity and prolonged need for ICU care.[5-8] However, the role of nutrition in the care for critically ill COVID-19 patients is not well understood.

Therefore, we conducted this multicenter, ambidirectional cohort study in the cities of Wuhan and Jingzhou, both located in the Hubei province, to provide insights into the role of nutrition in the care of critically ill COVID-19 patients.

METHODS

Study design and patients

This is a multicenter, ambidirectional cohort study conducted on March 6th, 2020, at 11 hospitals located in Wuhan (10 hospitals) and Jingzhou (1 hospital). A waiver was obtained from the institutional review board before data collection. All the included ICUs or wards in this study were designated centers for treating COVID-19 patients. Data collection was performed via written case report forms. All patients with a diagnosis of critical COVID-19 in the study sites at 00:00, March 6th, 2020, were included for this study.

Definitions

Critical COVID-19 was defined according to the latest Chinese expert consensus definition (Ver 7.0), and all patients had severe acute respiratory distress syndrome (ARDS) requiring intubation and invasive mechanical ventilation, exhibited cardiovascular failure, or had other organ failure requiring ICU admission. Gastrointestinal function was categorized into four levels, from normal to failure, using the acute gastrointestinal injury (AGI) grading system.[9] Original body weight was the bodyweight before hospital admission and was reported by the patients or their relatives. The estimated energy target was calculated accordingly using the equation target energy = original body weight (kg)* 25 kcal/kg".

Data collection

Demographic and clinical characteristics including Acute Physiology and Chronic Health Evaluation II (APACHE II) score, modified nutrition risk in critically ill (mNUTRIC) score,[10] and sequential organ failure assessment (SOFA) score of the study patients on March 6th, 2020 (hereafter referred to as "the study enrolment day") were recorded. The vital status of the study subjects was followed up 28 days after study enrolment. Routine laboratory tests were recorded, for example, C-reactive protein (CRP), white blood count (WBC), procalcitonin (PCT), albumin. Volume and energy density of enteral nutrition (EN) were documented, so were the parenteral nutrition (PN) prescriptions. The date when EN and PN were initiated was retrospectively recorded, but details regarding nutritional practice were only documented on the study enrolment day.

Statistical analysis

Data were analyzed using SPSS for Windows version 18 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as median (interquartile or range) as indicated and analyzed using Mann-Whitney U test. Categorical data were expressed as the absolute number (proportion) and compared with Pearson's chi-square or Fisher exact T test when appropriate. A difference with a two-tailed $p<0.05$ was considered statistically significant.

RESULTS

A total of 44 patients were identified and enrolled, of whom 36 were alive on day 28 follow-up (April 3th, 2020), as presented in Figure 1. The demographic and

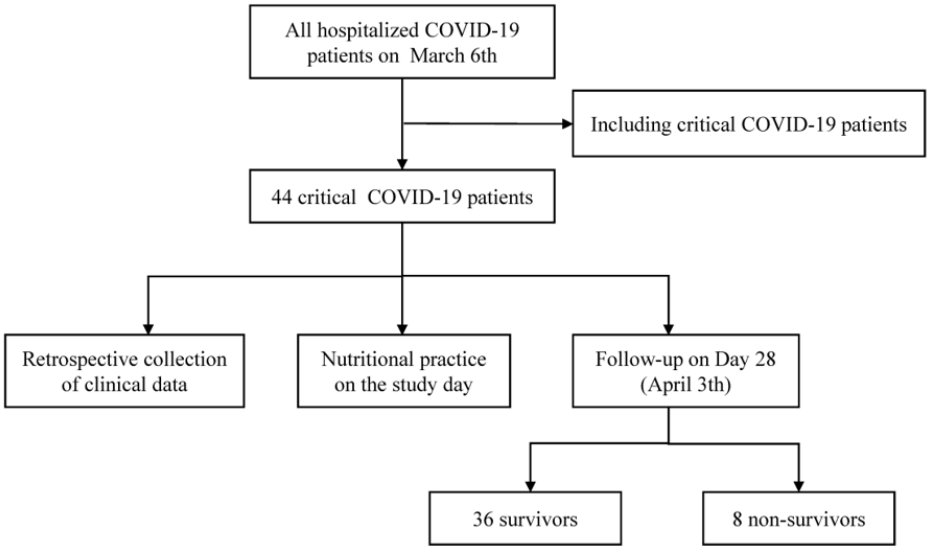

Figure 1. Study patient flow.

Table 1. Demographic and clinical characteristics of patients with COVID-19

Measures	Study patients (n=44)
Age, years	63 (57-70)
Male, No. (%)	27 (61.4)
Interval from admission to study day, d	24 (13-26)
Interval between ICU admission and study day, d	15 (9.75-24)
Pre-existing comorbidities, No. (%)	
Hypertension	22 (50)
Coronary heart disease	5 (11.4)
Diabetes	8 (18.2)
Chronic kidney disease	2 (4.5)
Chronic obstructive pulmonary disease	3 (6.8)
Chronic heart failure	1 (2.3)
Malignancy	1 (2.3)
Cirrhosis	1 (2.3)
Neurological disease	7 (2.3)
Gastrointestinal symptoms at admission, No. (%)	
Diarrhea	2 (4.5)
Abdominal distension	3 (6.8)
Abdominal pain	2 (4.5)
Complications during hospital stay, No. (%)	
Secondary infection	4 (9.1)
Acute kidney injury	6 (13.6)
Acute myocardial injury	10 (22.7)
Shock	11 (25)
Acute liver injury	5 (11.4)
Coagulation disorders	10 (22.7)
Others	9 (20.5)
GCS score on the study day	15 (12-15)
APACHE II score on the study day	13 (10-16.5)
SOFA score on the study day	5 (3-8)
mNUTRIC score on the study day	3 (2-5)
Laboratory measures on the study day	
CRP, μg/L	62 (26.5-124)
WBC, $x10^9$/L	9.1 (7.2-13.6)
PCT, ng/L	0.35 (0.17-1.35)
Antivirus drugs, No. (%)	
Lopinavir/ritonavir	1 (2.3)
Ribavirin	3 (6.8)
Chloroquine	1 (2.3)
Arbidol	6 (13.6)
Respiratory support on the study day, No. (%)	
Nasal cannula	1 (2.2)
Mask	4 (9.1)
High-flow nasal cannula	4 (9.1)
Non-Invasive mechanical ventilation	9 (20.5)
Invasive mechanical ventilation	26 (59.1)

ICU: intensive care unit; GCS: glasgow coma scale; APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; mNUTRIC: modified nutrition risk in the critically ill; CRP: C-reactive protein; WBC: while blood cell; PCT: procalcitonin.
Data are presented as n (%) or median (interquartile range).

clinical characteristics of the study subjects are shown in Table 1. The median interval from hospital admission and ICU entry to the study enrolment day were 24 days (range, 3 to 36 days) and 15 days (range, 3 to 32 days), respectively. Fifty percent (22 of 44) of patients had a history of hypertension and 59% (26 of 44) required invasive mechanical ventilation (IMV) on the study enrolment day.

For nutritional practice, as shown in Table 2, 75% (33 of 44) of the study subjects received EN or PN on the study enrolment day, either alone or in combination. Ten of the remaining eleven patients received oral intake. Only one patient was fasting on the study day due to intolerance to EN and inability to initiate oral intake. None of these 11 patients died on day 28 after study enrolment. Eight of the ten patients (80%) receiving oral intake alone required non-invasive mechanical ventilation (NiMV) on the study enrolment day.

For EN implementation, gastric feeding with a continuous pump was the most common approach for nutritional therapy accounting for 97% (29 of 30) of the EN fed patients. PN was provided to 25% (11 of 44) of patients with a median amount of energy provided by PN of 500kcal (inter-quartile range, 100 to 950kcal). The target achievement rate in the patients receiving EN and/or PN was 69.7% (23 of 33).

With regards to gastrointestinal function, 63% (28 of 44) of patients were categorized as mild injury (AGI I) and the rest (16 of 44) were scored as moderate (AGI II). Feeding-related complications such as nausea and aspiration were infrequent, with a prevalence of 11.4% (5 of 44)

Table 2. Measures of nutritional support procedure

	Study patients (n=44)
Mean time from admission to EN initiation, d	1 (0-7)
Mean time from admission to start PN, d	17 (10-26)
Mean energy delivered in fed patients† on the study day, kcal	
EN	1300 (1000-1500)
PN	500 (100-950)
Proportion of fed patients† on the study day	
EN alone	22 (50)
PN alone	3 (6.8)
EN and PN	8 (18.2)
Target-reaching rate in fed patients† on the study day, No. (%)	23/33 (69.7)
Gastrointestinal function, No. (%)	
AGI-I	28 (63.6)
AGI-II	16 (36.4)
AGI-III	0 (0)
AGI-IV	0 (0)
EN routes, No. (%)	
Gastric	28 (63.6)
Post-pyloric	2 (4.5)
EN delivery method, No. (%)	
Continuous pump	29 (65.9)
By gravity	1 (2.3)
Position, No. (%)	
Head of bed ≥30°	3 (6.8)
Head of bed <30°	21 (47.7)
Prone position	2 (4.5)
Presence of nausea, No. (%)	
Yes	5 (11.4)
No	39 (88.6)
Presence of vomiting, No. (%)	
Yes	10 (22.7)
No	34 (77.2)
Presence of aspiration, No. (%)	
Yes	3 (6.8)
No	41 (93.2)
Presence of abdominal pain, No. (%)	
No	19 (43.2)
Persistent	1 (22.7)
Self-resolution	1 (22.7)
Unable to judge	23 (52.3)
Presence of abdominal distension, No. (%)	
No	18 (40.9)
Mild	10 (22.7)
Obvious	2 (4.5)
Unable to judge	14 (31.8)
Bowel sound, No. (%)	
Hyper	3 (6.8)
Hypo	5 (11.4)
Normal	21 (47.7)
Unable to judge	15 (34.1)
Frequency of stool on the study day	1 (1-2)
Stool description, No. (%)	
Shaped soft	17 (38.6)
Loose	1 (2.3)
Watery	16 (36.4)
Albumin, g/L	30.3 (27.3-34.5)

EN: enteral nutrition; PN: parenteral nutrition; AGI: acute gastrointestinal injury.
Data are presented as n (%) or median (interquartile range).
†Fed patients refer to patients receiving either EN or PN or both. Patients had oral intake only were excluded.

and 6.8% (3 of 44), respectively.

When comparing the non-survivors with the surviving patients, a significant difference could be detected in terms of the APACHE II score, SOFA score, and modified NUTRIC scores on the study enrolment day (Table 3). More patients received EN combined with supplemental PN in non-survivor group. No difference could be seen in terms of other nutritional practice measures.

DISCUSSION

It has been recommended that nutrition therapy should be appropriately implemented in patients with COVID-19,

Table 3. Characteristics and nutritional practice of survivors and non-survivors

	Non-survivors (n=8)	Survivors (n=36)	*p* value
Age, years	65 (59-74)	65 (56-70)	0.526
Male, No. (%)	5 (62.5)	22 (61.1)	0.942
Interval from admission to study day, d	26 (25-27)	21.5 (12-25)	0.15
Interval between ICU admission and study day, d	22 (11.75-25)	15 (9.75-23.75)	0.189
Pre-existing comorbidities, No. (%)			
Hypertension	5 (62.5)	17 (47.2)	0.696
Coronary heart disease	1 (12.5)	4 (11.1)	1
Diabetes	1 (12.5)	7 (19.4)	1
Chronic kidney disease	0 (0)	2 (5.6)	1
Chronic obstructive pulmonary disease	0 (0)	3 (8.3)	1
Chronic heart failure	0 (0)	1 (2.8)	1
Malignancy	0 (0)	1 (2.8)	1
Cirrhosis	0 (0)	1 (2.8)	1
Neurological disease	1 (12.5)	6 (16.7)	1
Gastrointestinal function, No. (%)			0.964
AGI-I	5 (62.5)	23 (63.9)	
AGI-II	3 (37.5)	13 (36.1)	
AGI-III	0 (0)	0 (0)	
AGI-IV	0 (0)	0 (0)	
Laboratory measures on the study day			
CRP, μg/L	123 (60.9-165)	55.9 (22.8-110)	0.122
WBC, $x10^9$/L	9.7 (7.22-11.1)	8.83 (7.03-13.7)	0.848
Albumin, g/L	29.1 (27.2-40.4)	30.4 (27.2-34.6)	0.863
Respiratory support on the study day, No. (%)			0.204
Nasal cannula	0 (0)	1 (2.8)	
Mask	0 (0)	4 (11.1)	
High-flow nasal cannula	0 (0)	4 (11.1)	
Non-invasive mechanical ventilation	0 (0)	9 (25)	
Invasive mechanical ventilation	8 (100)	18 (50)	
Mean time from admission to start EN, d	7 (0.5-16)	0.5 (0-7.25)	0.627
Mean time from admission to start PN, d	17 (12-27)	18.5 (5.5-24.5)	0.464
Approach of nutrition therapy on the study day			0.048
Oral alone	0 (0)	10 (27.8)	
EN alone	3 (37.5)	19 (52.8)	
PN alone	1 (12.5)	2 (5.6)	
EN and PN	4 (50)	4 (11.1)	
Fasting	0 (0)	1 (2.8)	
Mean energy delivered in fed patients† on the study day, kcal			
EN	1000 (600-1500)	1300 (1000-1500)	0.279
PN	500 (100-975)	675 (177.5-950)	0.853
Target-reaching rate in fed patients† on the study day, No. (%)	4/8 (50)	19/25 (76)	0.342

CRP: C-reactive protein; WBC: while blood cell; EN: enteral nutrition; PN: parenteral nutrition; AGI: acute gastrointestinal injury
Data are presented as n (%) or median (interquartile range).
†Fed patients refer to patients receiving either EN or PN or both. Patients had oral intake only were excluded.

especially for those critically ill cases who are likely to have a substantial ICU stay,[11,12] but information regarding nutritional practice in COVID-19 patients is scarce. The results of this ambidirectional cohort study offer a glimpse at the current nutritional practice for the management of these patients. We demonstrate that gastric tube-feeding EN was the preferred route and method for nutrient delivery. PN and oral intake were also frequently provided.

Our results showed that only one patient was not fed on the study day, reflecting that the importance of nutritional support was well recognized by Chinese physicians when treating critical COVID-19. Based on the recomendations from both European Society for Parenteraland Enteral Nutrition (ESPEN), and Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN),[4,13] the target reaching rate is not satisfying in the study COVID-19 patients considering the fact that most of them had been hospitalized for more than a week on the study day. The real rate can be even worse because those on NiMV can hardly have adequate food intake, but we can not calculate the exact calories of the set meals they consumed. However, as Marik et al's meta-analysis revealed, the deleterious effect of hypocaloric feeding on clinical outcomes may be overestimated, as it was mostly built on the basis of observational studies.[14] Moreover, as we used original body weight reported by patients or their family members instead of the actual weight to exclude disease-related weight change, which can be large in some ICU patients, recall bias is inevitable. According to the results, no difference in target reaching rate was detected between survivors and non-survivors. We also failed to find any association between the pattern of feeding on the study day and the clinical outcomes, as the results showed that disease severity rather than nutritional practice is the prima-

ry determinant of mortality.

Impairment of gastrointestinal function and increased intra-abdominal pressure were common findings in the general ICU population, and it is a major adverse factor impeding EN implementation.[15,16] Our previous study showed that more than 10% of the study patients suffered from AGI III or IV,[15] which indicates gastrointestinal failure.[9] However, our findings suggested that even the critical type of COVID-19 seldom affects the function and mobility of the alimentary tract, which possibly makes implementing EN easier in these patients. Therefore, the relatively lower target-reaching rate we found in this study may be mostly ascribed to the lack of consciousness of adequate nutritional practice. However, no outcome-related detrimental effects could be confirmed from our data.

The clinical value of PN, especially in the supplemental form, was reassessed recently, and the latest ESPEN guideline recommended that supplemental PN could benefit critically ill patients in case of prolonged nutritional deficit.[4] Several studies have shown that negative energy balance could adversely impact the critically ill with increasing morbidity.[7,8] However, early prescription of PN to achieve the full provision of energy may not be helpful, because early stress-related endogenous production of energy substrate could be intense during the first a few days. Moreover, an early and large amount of glucose delivery might be correlated with increased morbidity rather than clinical benefits.[17] According to our results, utilization of PN is not uncommon in the study COVID-19 patients suggesting that underfeeding was well recognized by their treating physicians, and most of the PN was prescribed together with EN feeding in a supplemental form. However, the initial timing of PN was relatively later, which could probably be attributed to the progressively evolving disease.

There are certain limitations of this study we need to address here. The present study has a limited follow-up period, which may significantly impact the generalizability of our results. In addition, the study patients were identified from 11 different hospitals, which may give rise to great variability among the treating physicians. However, inclusion of patients from 11 different hospitals may also improve generalizability.

In conclusion, EN feeding was the mainstream in the management of critical COVID-19 patients, and PN and oral intake were also frequently applied. Energy delivery was suboptimal in this study and may require more attention. However, we did fail to find any association between the pattern of feeding on the study enrolment day and the clinical outcomes, as the results showed that disease severity rather than nutritional practice is the primary determinant of mortality. Additional prospective studies are required in this important patient group to help inform future practice.

AUTHOR DISCLOSURES

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