

Nutrition support practices for critically ill patients with severe acute respiratory syndrome coronavirus-2: A multicentre observational study in Singapore

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ABSTRACT

Introduction: To improve the nutritional care and resource allocation of critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), we described their characteristics, treatment modalities and clinical outcomes, and compared their nutrition interventions against the American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations.

Methods: This was a retrospective observational study conducted in 5 tertiary hospitals in Singapore. Characteristics, treatment modalities, clinical outcomes and nutrition interventions of critically ill patients with SARS-CoV-2 who received enteral and parenteral nutrition were collected between January and May 2020.

Results: Among the 83 critically ill patients with SARS-CoV-2, 22 (28%) were obese, 45 (54%) had hypertension, and 21 (25%) had diabetes. Neuromuscular blockade, prone therapy and dialysis were applied in 70% (58), 47% (39) and 35% (29) of the patients, respectively. Refeeding hypophosphataemia and hospital mortality occurred respectively in 6% (5) and 18% (15) of the critically ill patients with SARS-CoV-2. Late enteral nutrition and cardiovascular comorbidities were associated with higher hospital mortality (adjusted relative risk 9.00, 95% confidence interval [CI] 2.25–35.99; 6.30, 95% CI 1.15–34.40, respectively). Prone therapy was not associated with a higher incidence of high gastric residual volume (≥ 250 mL). The minimum caloric (15kcal/kg) and protein (1.2g/kg) recommendations of ASPEN were achieved in 54% (39) and 0% of the patients, respectively.

Conclusion: The high obesity prevalence and frequent usage of neuromuscular blockade, prone therapy, and dialysis had considerable implications for the nutritional care of critically ill patients with SARS-CoV-2. They also did not receive adequate calories and protein. More audits should be conducted to refine nutritional interventions and guidelines for this ever-evolving disease.

Ann Acad Med Singap 2022;51:329-40

Keywords: COVID-19, critical illness, energy intake, enteral nutrition, nutrition support, protein intake

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CLINICAL IMPACT

What is New

- A large proportion of intensive care unit (ICU) COVID-19 patients in Singapore were obese, had diabetes, and received neuromuscular blockade, prone therapy and dialysis.
- Late enteral nutrition (>36 hours) was associated with higher hospital mortality.
- Refeeding hypophosphataemia occurred in 6% of ICU COVID-19 patients.
- Proning was not associated with a higher incidence of high gastric residual volume.

Clinical Implications

- Half and none of ICU COVID-19 patients met their minimal caloric and protein goals, respectively. Therefore, clinicians should pay close attention to the nutrition adequacy of these patients.

INTRODUCTION

Within 3 weeks of the World Health Organization declaring the COVID-19 pandemic on 11 March 2020, the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) developed a set of nutrition guidelines that addresses issues on nutrition assessment; timing and feeding route; caloric and protein doses; enteral nutrition (EN) formula selection; monitoring; and feeding practices during prone and extracorporeal membrane oxygenation therapies for critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).¹ Singapore has one of the lowest case fatality rates, and this may be attributed to practices such as early intubation, lung protective ventilatory strategies and good general supportive care.²

With an increased number of SARS-CoV-2 patients admitted to intensive care units (ICUs) globally, attention is given to better care, including nutrition. Previous studies have identified barriers in providing nutrition to this vulnerable group, including unpredictable clinical courses and fear of aspiration.³ In this regard, we recognised that audit of local practices would make clinicians aware of the management gap, if any. There is currently only 1 local study (single-centre case series of 8 patients) that described the nutritional care of SARS-CoV-2 critically ill patients.⁴ Therefore, we conducted a multicentred observational study to describe the characteristics, treatment modalities, and clinical outcomes of SARS-CoV-2 critically ill patients; and

compare the nutrition support practices of Singapore against the SCCM/ASPEN recommendations.

METHODS

This was a retrospective audit of 5 tertiary hospitals in Singapore. Consecutive patients diagnosed with SARS-CoV-2 (confirmed by reverse-transcriptase–polymerase chain reaction test) and admitted to the ICU between January and May 2020 were screened for eligibility. Patients who were ≥ 21 years old and received non-volitional nutrition support such as EN and/or parenteral nutrition (PN) in the first 14 days of ICU admission were enrolled. Patients whose sole source of nutrition was peroral in the first 14 days of ICU admission were excluded. All patients were followed up to hospital discharge unless death occurred earlier. The Domain Specific Review Board approved this study (NHG DSRB Ref: 2020/00795), and the requirement of informed consent was waived.

Data collection

All data required were extracted from the electronic medical records of each hospital in a standardised password-protected Excel file. Data were grouped into categories of demographics; anthropometry; comorbidities; disease severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II], Sequential Organ Failure Assessment [SOFA] and modified Nutrition Risk in Critically Ill score [mNUTRIC]⁵); treatment modalities (e.g. extracorporeal membrane oxygenation, dialysis, prone therapy and neuromuscular blockade); nutrition practices (e.g. time from ICU admission to commencement of EN, and malnutrition assessment); caloric and protein intake during exclusive EN and/or PN from ICU admission to a maximum of 14 days unless death occurred earlier (i.e. calories and protein intake contributed by dextrose-containing intravenous fluids, propofol, protein modular and enteral and parenteral formulas); episodes of high gastric residual volume (high-GRV) (≥ 250 mL); duration of mechanical ventilation, ICU and hospital admission in survivors; and ICU and hospital mortality.

To compare our practice (Supplementary Table S1 in online Supplementary Material) with the SCCM/ASPEN recommendations,¹ additional data were collected. Specifically, exposure to early EN (≤ 36 hours from ICU admission); mean arterial pressure during the initiation of EN; prescription of caloric goal (indirect calorimetry [IC] versus weight-based formula); choice of the enteral and parenteral formula; incidence of diarrhoea (i.e. absence of laxative given 1 day before defecation of ≥ 3 stools rated as type 6–7 on the Bristol

Stool Scale/day or the utilisation of a rectal tube); measurement of serum triglyceride in patients exposed to propofol and/or PN; and head elevation of at least 10–25° during prone therapy.

Statistical analysis

Normality was assessed by the Shapiro-Wilk test. Data were summarised as mean and standard deviation (SD) (normally distributed continuous data), median and interquartile range (IQR) (non-normally distributed continuous data), or counts and percentages (categorical variables). They were compared using Student's t-test, Mann-Whitney U test, analysis of variance, Kruskal-Wallis H test, or chi-square test, as appropriate. To compare patients' caloric and protein intake from day 1 to day 7 with the SCCM/ASPEN recommendations, one-sample t-tests were carried out. To determine if prone therapy was associated with a higher incidence of high-GRV (≥ 250 mL), episodes of high-GRV and exposure to prone therapy were compared with Student's t-test in all patients. After that, in patients exposed to prone therapy, episodes of high-GRV on prone-day versus non-prone-day were compared with the Wilcoxon signed-rank test. To determine if EN formula containing fibre (EN-Fibre) was worse tolerated compared to fibre-free formula, the median exposure period to EN-Fibre was first determined, and patients below and above the median were classified as "not exposed" and "exposed", respectively. Thereafter, the number of high-GRV episodes and diarrhoea-days per 100 EN days were compared between patients who were "not exposed" and "exposed" using one-way analysis of covariance, adjusting for APACHE and diabetes. Modified Cox regression⁶ with backward elimination was used to determine the baseline parameters associated with hospital mortality. Statistical analyses were performed using SPSS Statistics software version 20.0 (IBM Corp, Armonk, US); all tests were two-sided, and P value < 0.05 was considered significant. Multiple testing correction was not applied, and P values should be interpreted as exploratory.

RESULTS

Eighty-three patients were enrolled, and their characteristics across the hospitals were generally similar (Table 1). Majority were either overweight (29/80, 36.3%) or obese (22/80, 27.5%) (3 missing data). Most of them had comorbidities such as hypertension (45, 54.2%) and diabetes (21, 25.3%). Disease severity was similar across the hospitals (mean [SD]: APACHE II 19.4 [9.8], SOFA 7.0 [4.5], and mNUTRIC 4.1 [2.0]) except for Hospital B, which had significantly lower

APACHE (14.8 [7.7]), SOFA (5.4 [3.3]), and mNUTRIC (3.4 [1.8]) scores.

Treatment modalities such as dialysis, neuromuscular blockade, and prone therapy were common. Across the hospitals, 1 in 3 patients (34.9%) required dialysis with a median duration of 4.0 (IQR 1.5–6.0) days; 7 in 10 patients (69.9%) received neuromuscular blockade with a median duration of 4.0 (IQR 2.0–8.0) days; and 1 in 2 patients (47.0%) received prone therapy with a median duration of 4.0 (IQR 2.0–6.0) days (Table 1). Two patients (2.4%) received extracorporeal membrane oxygenation therapy with a duration of 7 and 14 days, respectively.

Nutrition-related results

At ICU admission, 9 patients (10.8%) were kept on peroral feeding for ≥ 2 days, and their median EN start time was 4.0 (IQR 4.0–5.5) days (Table 2). Compared to other patients who either received EN or PN ($n=74$), they had significantly lower disease severity scores (mean [SD]: APACHE II 9.3 [4.1], SOFA 2.8 [2.2], and mNUTRIC 2.9 [1.2]); higher exposure to prone therapy (88.9% vs 41.9%); longer duration of neuromuscular blockade (median [IQR] 7.5 [6.0–9.5] vs 4.0 [2.0–6.0]); and higher mortality (55.6% vs 13.5%).

Seventy-three patients were first exposed to EN in the first 2 days of ICU admission because most of them were mechanically ventilated (67, 91.8%) during this period. The caloric and protein intake of these patients are shown in Figs. 1 and 2. Standard, diabetes-specific, and high-protein renal enteral formulas were commonly prescribed (Fig. S1 in Supplementary Material). Two patients (2.4%) received PN, of whom 1 also received EN. In both cases, PN was given for 1 day. No patients had a nasojejunal tube inserted. Refeeding hypophosphataemia was present in 5 patients (6.0%) (Table 1).

Enteral feeding intolerance was determined by the incidence of high-GRV and diarrhoea (Table 1). High GRV incidences mostly occurred in the first 4 days of ICU admission (Fig. S2 in Supplementary Material). High-GRV was also not associated with exposure to EN-Fibre after adjusting for APACHE and diabetes ($F(1,69)=0.406$, $P=0.526$). As for diarrhoea, there were 5.8 diarrhoea-days per 100 ICU days across the hospitals, and exposure to EN-Fibre is associated with lower mean diarrhoea-days per 100 EN days, ($F(1,69)=4.373$, $P=0.040$, adjusted for APACHE and diabetes).

Prone therapy is frequently carried out in the first 5 days of ICU admission (Fig. S2 in Supplementary Material). Compared to patients receiving EN without prone therapy (37), patients with EN and prone therapy

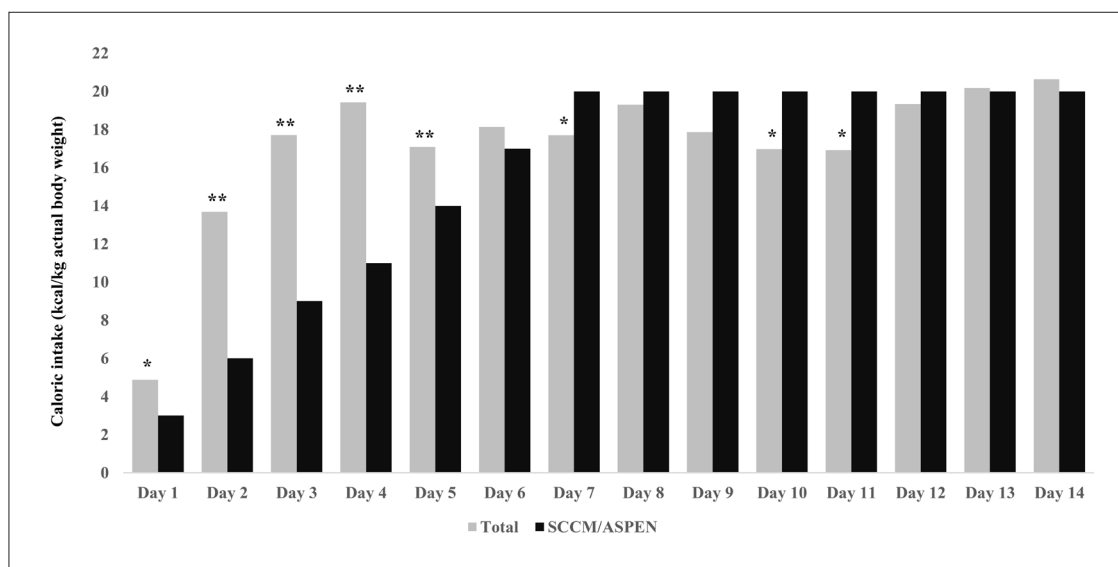


Fig. 1. Caloric intake of patients over 14 days.

SCCM/ASPEN: Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition

* $P < 0.05$, ** $P < 0.001$

had significantly higher episodes of high-GRV (median [IQR]: 0 [0] vs 0 [0–2], $P = 0.031$). In patients with EN and prone therapy ($n = 36$), the episodes of high-GRV on prone and non-prone days were similar (median [IQR]: 0 [0–0.1] vs 0 [0], $P = 0.113$).

In the modified Cox regression, cardiovascular comorbidities—i.e. congestive heart failure, myocardial infarction and angina (adjusted relative risk [RR]: 9.00, 95% CI 2.25–35.99, $P = 0.002$)—and late enteral feeding (>36 hours upon ICU admission) (adjusted RR 6.30, 95% CI 1.15–34.40, $P = 0.034$) were significantly associated with hospital mortality. Other parameters such as sex, APACHE II, admission source, hypertension, neurological comorbidities, renal disease, and oncological comorbidities were not significantly associated with hospital mortality.

Comparison with the SCCM/ASPEN COVID-19 recommendations

Among the 8 domains of the SCCM/ASPEN COVID-19 recommendations, the nutritional practices in Singapore were not in line with half of them. Specifically, these were in areas of baseline malnutrition assessment; achievement of caloric and protein targets; choice of EN formula used in the initial phase of critical illness; and monitoring (Table 3).

DISCUSSION

In this multicentre observational study, critically ill patients with SARS-CoV-2 had similar characteristics and clinical outcomes across multiple hospitals. They also received comparable treatment modalities and

nutrition support, suggesting that the cohort was a good representation of such patients in Singapore. The characteristics and treatment modalities used in these patients posed unique nutrition support challenges as 1 in 3 were obese, had diabetes and received dialysis; 1 in 2 received prone therapy; and 7 in 10 received neuromuscular blockade. These have considerable implications for caloric and protein dosing as well as EN formula choice that the ASPEN/SCCM guidelines have not comprehensively addressed.

Nutrition assessment

All participating sites did not assess baseline nutritional status because their routine assessment tool is the Subjective Global Assessment that requires a nutrition-focused physical examination. Of note, malnutrition diagnosed by the Subjective Global Assessment was associated with higher mortality risk in both non-SARS-CoV-2¹ and SARS-CoV-2⁷ critically ill patients. To minimise physical contact and the risk of nosocomial transmission, nutrition screening tools that do not require physical examination could be used to quantify malnutrition risk. Nutrition Risk Screening 2002 score ≥ 3 was associated with higher mortality risk in one prospective study ($N = 285$)⁷ but not in another retrospective study ($N = 286$).⁸

In the absence of a validated nutrition screening/assessment tool that has good prognostic value and can be conducted without physical assessment, the utility of baseline nutrition screening/assessment can be questioned. We lack robust evidence showing that higher

Table 1. Characteristics, clinical outcomes, treatment modalities, feeding practices and enteral feeding intolerances

Parameters	All (N=83)	Hospital A (n=21)	Hospital B (n=35)	Hospital C (n=10)	Hospital D (n=14)	Hospital E (n=3)	P
Age, mean (SD), years	58.0 (12.7)	56.1 (13.5)	59.6 (14.3)	60.0 (8.8)	54.6 (9.7)	65.7 (8.7)	0.513
Male, no. (%)	63 (75.9)	15 (71.4)	28 (80.0)	7 (70.0)	10 (71.4)	3 (100)	0.764
Ethnicity, no. (%)							0.346
Chinese	51 (61.4)	12 (57.1)	23 (65.7)	5 (50.0)	8 (57.1)	2 (100)	
Malay	11 (13.3)	1 (4.8)	3 (8.6)	4 (40.0)	3 (21.4)	0	
Indian	10 (12.0)	4 (19.0)	5 (14.3)	0	1 (7.1)	0	
Others	11 (13.8)	4 (19.0)	4 (11.4)	1 (10.0)	2 (14.3)	0	
Weight, mean (SD), kg	74.4 (15.4)	72.4 (13.5)	72.0 (16.3)	78.8 (12.3)	77.6 (17.4)	85.1 (17.7)	0.406
BMI, mean (SD), kg/m ² ^a	27.1 (5.0)	27.0 (4.3)	26.4 (5.9)	28.1 (2.8)	27.7 (5.1)	29.4 (6.1)	0.777
25.0–29.9	29 (36.3)	6 (33.3)	14 (40.0)	6 (60.0)	3 (21.4)	0	0.270
>30.0	22 (27.5)	4 (22.2)	8 (22.9)	3 (30.0)	5 (35.7)	2 (66.7)	0.487
Admission, no. (%)							
ED	26 (31.3)	14 (66.7)*	5 (14.3)	2 (20.0)	4 (28.6)	1 (33.3)	0.001
HD	3 (3.6)	0	0	0	3 (21.4)*	0	0.004
Ward	44 (53.0)	5 (23.8)*	22 (62.9)	8 (80.0)	7 (50.0)	2 (66.7)	0.019
Other hospitals	10 (12.0)	8 (9.5)	8 (22.9)	0	0	0	0.104
Comorbidities, no. (%)							
Diabetes	21 (25.3)	4 (19.0)	4 (22.9)	5 (50.0)	4 (28.6)	0	0.187
Hypertension	45 (54.2)	12 (57.1)	17 (48.6)	8 (80.0)	7 (50.0)	1 (33.3)	0.430
Cardiological	6 (7.2)	1 (4.8)	4 (11.4)	0	1 (7.1)	1 (33.3)	0.388
Neurological	4 (4.8)	2 (9.5)	1 (2.9)	1 (10.0)	0	0	0.600
Renal	8 (9.6)	1 (4.8)	3 (8.6)	2 (20.0)	2 (14.3)	0	0.641
Cancer	5 (6.0)	3 (14.3)	1 (2.9)	1 (10.0)	0	0	0.340
Disease severity scores, mean (SD)							
APACHE II	19.4 (9.8)	21.2 (11.6)	14.8 (7.7)*	24.6 (6.7)	25.4 (9.1)	15.3 (4.9)	0.001
SOFA	7.0 (4.5)	6.3 (5.1)	5.4 (3.3)*	8.4 (2.7)	10.5 (5.3)	8.7 (1.2)	0.003
mNUTRIC	4.1 (2.0)	4.0 (1.9)	3.4 (1.8)*	5.9 (1.8)	5.1 (1.8)	4.3 (2.3)	0.002

Table 1. Characteristics, clinical outcomes, treatment modalities, feeding practices and enteral feeding intolerances (Cont'd)

Parameters	All (N=83)	Hospital A (n=21)	Hospital B (n=35)	Hospital C (n=10)	Hospital D (n=14)	Hospital E (n=3)	P
Dialysis, no. (%)	29 (34.9)	7 (33.3)	12 (34.3)	2 (20.0)	8 (57.1)	0	0.226
Median (IQR), days	4.0 (1.5, 6.0)	1.0 (1.0, 10.0)	3.0 (2.0, 6.0)	3.0 (2.0, NA)	5.0 (1.8, 7.0)	NA	0.855
Neuromuscular blockade, no. (%)	58 (69.9)	11 (52.4)	429 (82.9)	3 (30.0)*	12 (85.7)	3 (100)	0.004
Median (IQR), days	4.0 (2.0, 8.0)	2.0 (2.0, 4.0)	6.0 (4.0, 8.0)	3.0 (1.0, NA)	3.0 (3.0, 4.0)	2.0 (1.0, NA)	0.056
Prone (%)	39 (47.0)	4 (19.0)	21 (60.0)*	4 (40.0)	9 (64.3)*	1 (33.3)	0.026
Median (IQR), days	4.0 (2.0, 6.0)	4.5 (2.5, 8.0)	6.0 (3.5, 7.0)	3.5 (2.0, 6.5)	3.0 (2.0, 3.5)	2.0 (2.0, 2.0)	0.079
Head elevated <10°, no. (%)	5 (12.8)	1 (25)	3 (14.3)	0	0	1 (100)*	0.032
Feeding practices							
Start of EN, no. (SD), hour	11.5 (10.2)	11.8 (11.8)	14.2 (10.4)	10.7 (7.2)	7.7 (9.5)	6.7 (2.1)	0.345
Early feeding, no. (%) ^b	70/73 (95.9)	19/20 (95.0)	24/26 (92.3)	10/10 (100)	14/14 (100)	3/3 (100)	0.506
MAP<65, no. (%)	3/73 (4.1)	20/20 (100)	2/26 (7.7)	10/10 (100)	1/14 (7.1)	0/3 (0)	0.628
Peroral ≥2 days, no. (%)	9/83 (10.8)	1/21 (4.8)	8/35 (22.9)	0	0	0	0.054
Parenteral nutrition, no. (%)	2/83 (2.4)	0	2/35 (5.7)	0	0	0	0.590
Feeding intolerance							
High-GRV, episodes/100 feeding days	7.7	17.4*	7.2	1.2	3.1	0.0	<0.001
Diarrhoea							
Patients, no. (%)	35 (42.2)	7 (33.3)	19 (54.3)	0	9 (64.3)*	0	0.005
Days/100 ICU days	5.8	8.5	5.4	0	30.8*	0	<0.001
Clinical outcomes							
RH, no. (%)	5 (6.0)	1 (4.8)	3 (8.6)	0	1 (7.1)	0	0.857
ICU mortality, no. (%)	15 (18.1)	2 (9.5)	10 (28.6)	0	3 (21.4)	0	0.158
Hosp mortality, no. (%)	15 (18.1)	2 (9.5)	10 (28.6)	0	3 (21.4)	0	0.158
ICU-LOS of survivors, median (IQR), days	11.0 (7.0, 21.8)	8.0 (6.0, 11.0)*	18.0 (8.0, 31.0)	8.5 (5.0, 15.0)	14.0 (11, 32.0)	19.0 (13.0, NA)	0.027
Hosp-LOS of survivors, median (IQR), days	31.0 (19.3, 44.0)	23.0 (17.0, 37.0)	31.0 (19.5, 67.0)	30.5 (15.0, 41.5)	39.0 (29.0, 48.0)	31.0 (17.0, NA)	0.119
MV of survivors, median (IQR), days	9.0 (5.0, 15.0)	7.0 (3.0, 10.0)	11.0 (5.5, 25.5)*	7.5 (3.0, 11.3)	12.0 (9.0, 15.0)*	10.0 (8.0, NA)	0.039
Tracheostomy, no. (%)	11 (13.3)	2 (9.5)	5 (14.3)	0	4 (28.2)	0	0.274

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; BMI: body mass index; ED: emergency department; EN: enteral nutrition; GRV: gastric residual volume; HD: high dependency ward; Hosp: hospital; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; MAP: mean arterial pressure (mmHg); mNUTRIC: modified Nutrition Risk in Critically Ill; MV: mechanical ventilation; NA: not available; RH: refeeding hypophosphataemia defined as serum phosphate <0.65 within 72 hours of feeding; SD: standard deviation; SOFA: Sequential Organ Failure Assessment

^a 3 missing data

^b Enteral nutrition started within 36 hours of admission to the intensive care unit

* $P<0.05$

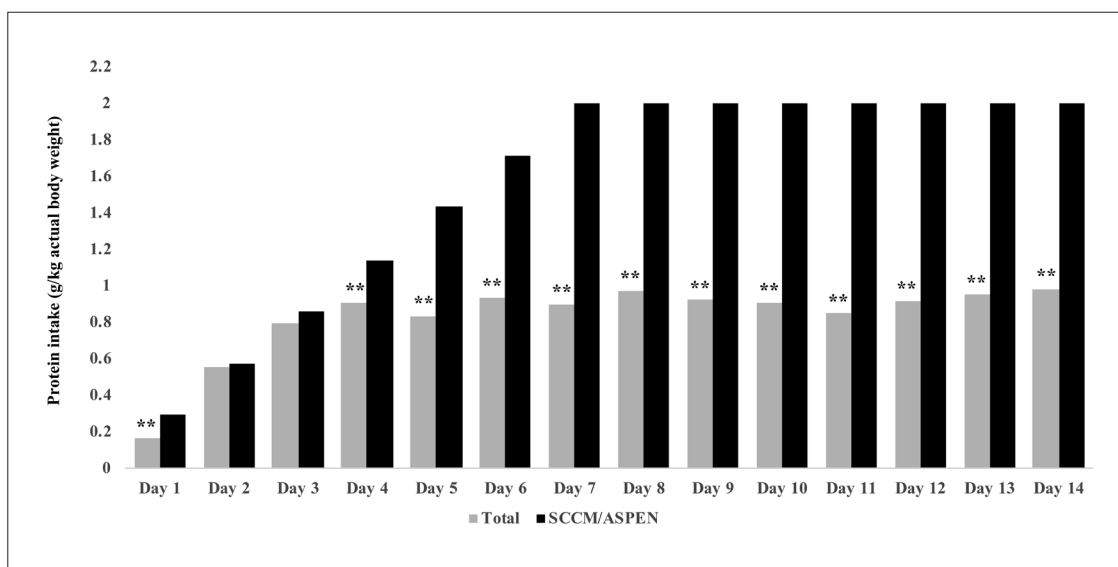


Fig. 2. Protein intake of patients over 14 days.

SCCM/ASPEN: Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition

** $P < 0.001$

caloric intake or more timely nutritional interventions can modify the poor clinical outcomes associated with baseline malnutrition.⁹ Furthermore, since well-nourished patients with severe illness can deplete their stores rapidly, early nutrition provision is essential regardless of baseline nutrition status. Perhaps the role of nutrition assessment should focus on identifying patients who may be harmed by rapid escalation of nutrition. This will include quantifying the risk of refeeding hypophosphataemia—6% in this study and 15% in another.¹⁰ In patients with hypophosphataemia, caloric restriction was demonstrated to reduce long-term mortality risk.¹¹ The National Institute of Health and Care Excellence guidelines¹² are commonly used to assess the risk of refeeding hypophosphataemia but require information such as diet and weight history—a challenging prospect to obtain from critically ill patients. Instead, one could focus on risk factors that do not rely on history taking such as the presence of hypokalaemia, hypophosphataemia and hypomagnesaemia; use of diuretics; and old age before the initiation of nutrition support,^{13,14} and provide protocolised caloric restriction to high-risk patients.¹¹

Timing and feeding route

In patients receiving peroral feeding, we did not measure caloric and protein intake from food. Many of them received awake prone therapy, and may potentially suffer from dyspnoea, anosmia and ageusia, which may lead to poor oral intake.¹⁵ EN was started on day

4 of ICU admission in most of these patients. Although they had significantly lower disease severity, their mortality rate was significantly higher than patients first exposed to EN in the initial 2 days of ICU admission. It is possible that early EN modulates immune responses, opposes dysbiosis, and maintains gut integrity.¹⁶ Although this is consistent with previous meta-analysis,¹⁷ our results should be interpreted with caution due to the small number of patients who received late EN ($n=3$).

Caloric dose

In this study, caloric goals were not established by IC as this technique may increase the healthcare providers' exposure to COVID-19. Furthermore, the use of IC lacks robust benefits for the heterogenous ICU population. A recent meta-analysis reported that IC-guided nutrition support resulted in an absolute mortality risk reduction of about 5.5%.¹⁸ Since 3 and 7 in 10 patients in our study were obese and received neuromuscular blockade, respectively, IC may be especially applicable to this population where estimating energy expenditure can be challenging.¹⁹⁻²¹ In addition, SARS-CoV-2 critically ill patients did not appear to have a uniform course of energy expenditure during their ICU admission; some patients had normal metabolism²² whereas others had hypermetabolism^{23,24} after week 3 and onwards in the ICU. Preliminary data suggest that the resolution of infection may reduce energy demand, and the cessation of isolation may be an important clinical landmark to re-evaluate energy

Table 2. Characteristics, treatment modalities, and clinical outcomes of patients who were placed on enteral nutrition versus peroral feeding in the first 2 days of intensive care unit admission

Parameters	All (N=83)	Enteral nutrition (n=74)	Peroral (n=9)	P
Age, no. (SD), years	58.0 (12.7)	57.8 (12.5)	61.2 (14.6)	0.444
BMI (SD), kg/m ² ^a	27.1 (5.0)	27.3 (5.0)	25.3 (5.4)	0.250
Comorbidities, no. (%)				
Diabetes	21 (25.3)	19 (25.7)	2 (22.2)	1.000
Hypertension	45 (54.2)	40 (54.1)	5 (55.6)	1.000
Cardiological	6 (7.2)	7 (9.5)	0	1.000
Neurological	4 (4.8)	3 (4.1)	1 (11.1)	0.374
Renal	8 (9.6)	7 (9.5)	1 (11.1)	1.000
Cancer	5 (6.0)	5 (6.8)	0	1.000
Disease severity				
APACHE II	19.4 (9.8)	20.7 (9.6)	9.3 (4.1)	<0.001
SOFA	7.0 (4.5)	7.5 (4.4)	2.8 (2.2)	<0.001
mNUTRIC	4.1 (2.0)	4.3 (2.1)	2.9 (1.2)	0.008
Clinical outcomes				
ICU mortality, no. (%)	15 (18.1)	10 (13.5)	5 (55.6)	0.008
Hosp mortality, no. (%)	15 (18.1)	10 (13.5)	5 (55.6)	0.008
ICU-LOS of survivors (IQR), days	11.0 (7.0, 21.8)	11.0 (7.0, 20.8)	22.0 (10.5, 30.5)	0.292
Hosp-LOS of survivors (IQR), days	31.0 (19.3, 44.0)	31.0 (19.3, 43.5)	53.5 (23.0, 92.3)	0.225
MV of survivors (IQR), days	9.0 (5.0, 15.0)	9.0 (5.0, 15.0)	11.5 (4.0, 24.3)	0.870
Dialysis, no. (%)	29 (34.9)	24 (32.4)	5 (55.6)	0.266
Median (IQR), days	4.0 (1.5, 6.0)	3.5 (1.3, 6.8)	5.0 (2.0, 6.0)	0.889
Neuromuscular blockade (%)	58 (69.9)	50 (67.6)	8 (88.9)	0.266
Median (IQR), days	4.0 (2.0, 8.0)	4.0 (2.0, 6.0)	7.5 (6.0, 9.5)	0.008
Prone, no. (%)	39 (47.0)	31 (41.9)	8 (88.9)	0.011
Median (IQR), days	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	6.0 (4.5, 7.0)	0.079

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II; BMI: body mass index; EN: enteral nutrition; Hosp: hospital; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; MV: mechanical ventilation; mNUTRIC: modified Nutrition Risk in Critically Ill; SD: standard deviation; SOFA: Sequential Organ Failure Assessment

^a 3 missing data

demands.²² In the above circumstances, healthcare providers can adopt a set of practical guidance for using IC in SARS-CoV-2 critically ill patients²⁵ so that appropriate caloric goals can be set for nutrition support.

The minimum caloric recommendation of SCCM/ASPEN was only met by 1 in 2 patients in this study. Of note, a recent review²⁶ and a newer version of the ASPEN guidelines²⁷ state that current evidence precludes

precise recommendations on the optimal caloric intake, and the latter should be based on clinical judgment. That said, insufficient micronutrients intake resulting from hypocaloric feeding should not be managed by high-dose supplementation.²⁸ Nevertheless, caloric intake may be improved by feeding protocols developed by a multidisciplinary team.⁹ For instance, the protocol can stipulate that EN can be safely started as soon as patients

Table 3. Nutrition recommendations of SCCM/ASPEN for critically ill patients with COVID-19 and the nutritional practice in Singapore

SCCM/ASPEN recommendation		Nutritional practice in Singapore
Assessment		
1	Perform nutrition assessment with minimal physical contact, and establish the risk of refeeding syndrome as well as the route and dose of nutrition support.	Malnutrition assessment was not performed at baseline across the hospitals.
Timing and finding route		
2	Initiate enteral nutrition within 36 hours of ICU admission or as soon as patient achieved adequate resuscitation (sustained mean arterial pressure of ≥ 65 mmHg).	Most patients (95.9%) received early EN, and their mean arterial pressure was > 65 mmHg when started on EN.
3	Start early parenteral nutrition in patients with sepsis or shock requiring escalating or multiple vasopressors or rising lactate levels.	Two patients received parenteral nutrition. One started on day 2 and the other on day 5 of ICU admission.
4	Prioritise continuous gastric feeding and use prokinetic agents to manage EFI. If EFI persists, consider bedside placement of post-pyloric tube.	Continuous gastric feeding was carried out in all patients on EN.
Caloric and protein doses		
5	Use weight-based equations to estimate energy requirements.	Caloric goals were estimated by weight-based equations, and IC was not used.
6	Initiate low-dose enteral nutrition and gradually advance to caloric goal (15–20 kcal/kg ABW) over the first week of critical illness.	- In the first 14 days of ICU admission, the mean caloric intakes across the hospitals were similar (Supplementary Table S1). - Caloric intake in the first 5 days was significantly higher than recommendations, whereas it was significantly lower on day 7 (Fig. 1). - By day 14, the mean (SD) caloric intake was 20.6 (6.9) kcal/kg ABW, and 54% of the patients received ≥ 15 kcal/kg ABW.
7	Initiate low-dose enteral nutrition and gradually advance to protein goal (1.2–2.0 g protein/kg ABW) over the first week of critical illness.	- In the first 14 days of ICU admission, the mean protein intakes across the hospitals were similar (Supplementary Table S1). - On most days (except for day 2 and day 3), protein intake was significantly lower than recommendations (Fig. 2). - By day 14, the mean (SD) protein intake was 0.98 (0.34) g/kg ABW, and no patients received ≥ 1.2 g protein/kg ABW.
8	If parenteral nutrition is necessary, conservative dextrose content and volume should be used in the early phase of critical illness.	In the patient who received early parenteral nutrition, dextrose contributed to 37% of the total caloric content.
Formula selection		
9	Use standard high protein ($\geq 20\%$ protein) polymeric isosmotic enteral formula at the early phase of critical illness, and at a later phase, consider adding fibre in the absence of significant gastrointestinal dysfunction.	- None of the hospitals used standard high protein ($> 20\%$) polymeric isosmotic enteral formula (Supplementary Fig. S1). - One in 4 received formulas containing fibre on the first week of EN feeding.
10	If parenteral nutrition is used, limit the use of pure soybean lipid emulsions and use mixed lipid emulsions instead.	None of the hospitals used pure soybean lipid emulsion for parenteral nutrition.
Monitoring		
11	To monitor feeding tolerance, use parameters such as stool frequency and flatulence, and avoid using gastric residual volume.	All hospitals routinely checked gastric residual volume and stool frequency.
12	In patients on parenteral nutrition and/or propofol, monitor serum triglyceride levels early in their course of therapy to help distinguish secondary haemophagocytic histiocytosis from propofol-related hypertriglyceridaemia.	Serum triglyceride was measured in 30.6% (n=15) of the patients who received propofol or parenteral nutrition, and the mean (SD) was 2.29 (1.24) mmol/L.

Table 3. Nutrition recommendations of SCCM/ASPEN for critically ill patients with COVID-19 and the nutritional practice in Singapore (Cont'd)

SCCM/ASPEN recommendation		Nutritional practice in Singapore	
Feeding in the prone position			
13	Although the provision of enteral nutrition during prone positioning is not associated with increased risk of gastrointestinal or pulmonary complications, the head of the bed should be elevated to at least 10–25° to decrease the risk of aspiration of gastric content, facial oedema, and intra-abdominal hypertension.	Most patients’ head was elevated >10° (Table 2).	
Nutrition therapy during extracorporeal membrane oxygenation			
14	Consider early trophic enteral feeding and gradually increase to goal over the first week of critical illness.	One of 2 patients received trophic enteral feeding.	
15	Monitoring for enteral feeding intolerance closely.	Gastric residual volume and stool frequency were monitored.	

ABW: actual body weight; EFI: enteral feeding intolerance; EN: enteral nutrition; IC: indirect calorimetry; ICU: intensive care unit; SD: standard deviation

achieved haemodynamic stability, and in patients who are on neuromuscular blockade and do not have severe gastrointestinal dysfunction.²⁶

Protein dose

No patient met the minimal protein recommendation in this study. This is especially concerning since 1 in 3 received dialysis, and such therapy depletes protein.²⁹ Furthermore, the mean duration of mechanical ventilation could be >10 days in some centres; when combined with neuromuscular blockade and steroid use, these can pose as risk factors for ICU-acquired weakness.³⁰ Therefore, more efforts should be made to meet protein goals, especially when a recent meta-analysis showed that higher protein provision significantly attenuates muscle loss.³¹ Nevertheless, all hospitals in this study provide additional protein given in boluses; this method of protein provision has the potential to benefit muscle health if targets are achieved. There is recent evidence that bolus provision of protein may attenuate muscle catabolism better than continuous feeding.³²

Formula selection

One-third of the patients in this cohort have type 2 diabetes mellitus, and since a low carbohydrate EN formula may improve glycaemic control,³³ 23% of the patients received diabetes-specific EN formula. Of note, all diabetes-specific formulas used in this study contain fibre, and providing such EN formula at the initial stage of critical illness is not in line with the SCCM/ASPEN guidelines.¹ However, we did not observe EN intolerances in patients who received diabetes-specific EN formula (containing fibre), but noted a significantly lower incidence of diarrhoea. This is

congruent with a recent systematic review demonstrating that EN formula containing fibre is associated with a significantly lower incidence of diarrhoea.³⁴

Monitoring

All the included hospitals did not adopt the recommendation of omitting GRV measurement. Of note, there is evidence^{35,36} that consistently demonstrated that high-GRV is a surrogate marker for delayed gastric emptying. Therefore, this parameter should be monitored to determine whether complex investigations or therapeutic interventions (e.g. prokinetic agents) are warranted.³⁵ Our data suggest that GRV can be routinely monitored during the initial phase of ICU admission, albeit less frequently or discontinued at a later phase because the frequency of high-GRV appeared to be heightened during the first 4 days of EN, an observation that coheres with large international data.³⁷ A large proportion of patients received prone therapy when high-GRV is a common concern.¹ However, our study does not support this. In our study, patients who received prone therapy had a significantly higher incidence of high-GRV than patients who were never prone. However, this could be explained by higher disease severity and not prone therapy per se. The poor association between prone therapy and high-GRV is further discussed in a recent review.²⁶

Besides high-GRV, diarrhoea may be a sign of EN intolerance. There is a paucity of data on the prevalence of diarrhoea in SARS-CoV-2 critically ill patients since most studies included non-critically ill patients and the pooled prevalence was 53.3%.³⁸ Although the diarrhoea prevalence in our study is similar to the meta-analysis,³⁸ it is considerably higher than reported in an ICU-specific

study (15%).³⁹ Similar to the latter, a limitation of our study is that we did not collect data about antibiotic exposure.

Serum triglycerides levels were not routinely monitored in patients who received propofol and PN in all included hospitals. Although hypertriglyceridaemia may not necessarily be associated with the dose and duration of propofol provided to SARS-CoV-2 critically ill patients, the incidence of hypertriglyceridaemia was as high as 1 in 2 patients.⁴⁰ Therefore, the guideline about serum triglyceride monitoring should be adopted to reduce the risk associated with hypertriglyceridaemia.

CONCLUSION

In this observational study of critically ill patients with SARS-CoV-2, we identified several aspects of nutrition that require further attention. With the long duration of mechanical ventilation and frequent usage of dialysis in such patients, more focus should be placed on increasing protein adequacy. Our observation also demonstrated that prone therapy and usage of EN-containing fibre may not be associated with EN feeding intolerances. Finally, the high prevalence of obesity and exposure to neuromuscular blockade prompt more studies about the role of indirect calorimetry in SARS-CoV-2 critically ill patients.

REFERENCES

- Martindale R, Patel JJ, Taylor B, et al. Nutrition therapy in critically ill patients with coronavirus disease 2019. *JPEN J Parenter Enteral Nutr* 2020;44:1174-84.
- Chew SY, Lee YS, Ghimray D, et al. Characteristics and outcomes of COVID-19 patients with respiratory failure admitted to a “pandemic ready” intensive care unit - Lessons from Singapore. *Ann Acad Med Singap* 2020;49:434-48.
- Suliman S, McClave SA, Taylor BE, et al. Barriers to nutrition therapy in the critically ill patient with COVID-19. *JPEN J Parenter Enteral Nutr* 2022;46:805-16.
- Chen DE, Goh SW, Chan HN, et al. Rehabilitation of intubated COVID-19 patients in a Singapore regional hospital with early intensive care unit and sustained post-intensive care unit rehabilitation. *Proc Singap Healthc* 2021;0:1-7.
- Rahman A, Hasan RM, Agarwala R, et al. Identifying critically-ill patients who will benefit most from nutritional therapy: further validation of the “modified NUTRIC” nutritional risk assessment tool. *Clin Nutr* 2016;35:158-162.
- Lee J, Tan CS, Chia KS. A practical guide for multivariate analysis of dichotomous outcomes. *Ann Acad Med Singap* 2009;38:714-9.
- Martinuzzi ALN, Manzanara W, Quesada E, et al. Nutritional risk and clinical outcomes in critically ill adult patients with COVID-19. *Nutr Hosp* 2021;38:1119-25.
- Czapla M, Juárez-Vela R, Gea-Caballero V, et al. The association between nutritional status and in-hospital mortality of COVID-19 in critically-ill patients in the ICU. *Nutrients* 2021;13:3302.
- Lew CC, Ong C, Mukhopadhyay A, et al. How to feed the critically ill—A review. *Ann Acad Med Singap* 2020;49:573-81.
- Farina N, Nordbeck S, Montgomery M, et al. Early enteral nutrition in mechanically ventilated patients with COVID-19 infection. *Nutr Clin Pract* 2021;36:440-8.
- Doig GS, Simpson F, Heighes PT, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. *Lancet Respir Med* 2015;3:943-52.
- National Institute for Health and Clinical Excellence. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition (CG32). London: National Collaborating Center for Acute Care, The Royal Surgeons of England; 2017.
- Wong GJ, Pang JG, Li YY, et al. Refeeding hypophosphatemia in patients receiving parenteral nutrition: prevalence, risk factors, and predicting its occurrence. *Nutr Clin Pract* 2021;36:679-88.
- Choi TY, Chang MY, Heo S, et al. Explainable machine learning model to predict refeeding hypophosphatemia. *Clin Nutr ESPEN* 2021;45:213-9.
- Ansu V, Papoutsakis C, Gletsu-Miller N, et al. Nutrition care practice patterns for patients with COVID-19—A preliminary report. *JPEN J Parenter Enteral Nutr* 2021;45:1174-8.
- McClave SA, Martindale RG, Rice TW, et al. Feeding the critically ill patient. *Crit Care Med* 2014;42:2600-10.
- Doig GS, Heighes PT, Simpson F, et al. 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.
- Duan JY, Zheng WH, Zhou H, et al. Energy delivery guided by indirect calorimetry in critically ill patients: a systematic review and meta-analysis. *Crit Care* 2021;25:88.
- Ridley E, Chapman M, Lambell K, et al. Obesity and nutrition in critical illness: the role of nutrition in obese critically ill patients and an overview of the clinical guidelines for nutrition provision in this patient population. *ICU Management and Practice* 2019:162-6.
- Mtaweh H, Soto Agüero MJ, Campbell M, et al. Systematic review of factors associated with energy expenditure in the critically ill. *Clin Nutr ESPEN* 2019;33:111-24.
- Karayianis D, Maragkoudi A, Mikropoulos T, et al. Neuromuscular blockade administration is associated with altered energy expenditure in critically ill intubated patients with COVID-19. *Clin Nutr* 2021;S0261-5614(21)00259-4.
- von Renesse J, von Bonin S, Held HC, et al. Energy requirements of long-term ventilated COVID-19 patients with resolved SARS-CoV-2 infection. *Clin Nutr ESPEN* 2021;44:211-7.
- Whittle J, Molinger J, MacLeod D, et al. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. *Crit Care* 2020;24:581.
- Niederer LE, Miller H, Haines KL, et al. Prolonged progressive hypermetabolism during COVID-19 hospitalization undetected by common predictive energy equations. *Clin Nutr ESPEN* 2021;45:341-50.
- Singer P, Pichard C, De Waele E. Practical guidance for the use of indirect calorimetry during COVID 19 pandemic. *Clin Nutr Exp* 2020;33:18-23.
- Al-Dorzi HM, Arabi YM. Nutrition support for critically ill patients. *JPEN J Parenter Enteral Nutr* 2021;45(S2):47-59.
- Compher C, Bingham AL, McCall M, et al. Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr* 2022;46:12-41.

28. Gudivada KK, Kumar A, Sriram K, et al. Antioxidant micronutrient supplements for adult critically ill patients: a bayesian multiple treatment comparisons meta-analysis. *Clinical Nutrition ESPEN* 2022;47:78-88.
29. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179-84.
30. Fan E, Cheek F, Chlan L, et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. *Am J Respir Crit Care Med* 2014;190:1437-46.
31. Lee ZY, Yap CSL, Hasan MS, et al. The effect of higher versus lower protein delivery in critically ill patients: a systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2021; 25:260.
32. Flower L, Haines RW, McNelly A, et al. Effect of intermittent or continuous feeding and amino acid concentration on urea-to-creatinine ratio in critical illness. *JPEN J Parenter Enteral Nutr* 2022;46:789-97.
33. Burslem R, Rigassio Radler D, Parker A, et al. Low-carbohydrate, high-fat enteral formulas for managing glycemic control in patients who are critically ill: A review of the evidence. *Nutr Clin Pract* 2022;37:68-80.
34. Cara KC, Beauchesne AR, Wallace TC, et al. Safety of using enteral nutrition formulations containing dietary fiber in hospitalized critical care patients: a systematic review and meta-analysis. *JPEN J Parenter Enteral Nutr* 2021;45:882-906.
35. Lew CCH, Lee ZY, Day AG, et al. Correlation between gastric residual volumes and markers of gastric emptying: A post hoc analysis of a randomized clinical trial. *JPEN J Parenter Enteral Nutr* 2022;46:850-7.
36. Chapman MJ, Besanko LK, Burgstad CM, et al. Gastric emptying of a liquid nutrient meal in the critically ill: relationship between scintigraphic and carbon breath test measurement. *Gut* 2011; 60:1336-43.
37. Heyland DK, Ortiz A, Stoppe C, et al. Incidence, risk factors, and clinical consequence of enteral feeding intolerance in the mechanically ventilated critically ill: an analysis of a multicenter, multiyear database. *Crit Care Med* 2021;49:49-59.
38. Maslennikov R, Poluektova E, Ivashkin V, et al. Diarrhoea in adults with coronavirus disease-beyond incidence and mortality: a systematic review and meta-analysis. *Infect Dis (Lond)* 2021; 53:348-60.
39. Osuna-Padilla I, Rodriguez-Moguel NC, Aguilar-Vargas A, et al. Safety and tolerance of enteral nutrition in COVID-19 critically ill patients, a retrospective study. *Clin Nutr ESPEN* 2021;43:495-500.
40. Kovacevic MP, Dube KM, Lupi KE, et al. Evaluation of hypertriglyceridemia in critically ill patients with coronavirus disease 2019 receiving propofol. *Crit Care Explor* 2021;3:e0330.