Early enteral nutrition may reduce the incidence of refeeding syndrome for patients with severe corona virus disease 2019 and high nutritional risk

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Received May 13, 2025; Accepted October 15, 2025

DOI: 10.3892/etm.2025.13029

Abstract. Nutritional therapy is an essential supportive intervention for patients with COVID-19 who are at high nutritional risk, although the optimal timing for initiating nutritional support remains unclear. The present study investigated the association between the initiation of enteral nutrition (EN) and the incidence of refeeding syndrome (RS) in severely ill patients with COVID-19 and high nutritional risk. Patients from Tongji Hospital (Wuhan, China), with a Nutrition Risk Screening-2002 score ≥3 and who received EN, were retrospectively analyzed and categorized into an early EN (EEN) group and a late EN (LEN) group based on the time-frame of EN initiation. Serum electrolyte levels were assessed on the third day after EN initiation to evaluate the incidence of RS. A total of 211 patients were included in this analysis (EEN group, n=125; LEN group, n=86). The mean time to EN initiation was 2 days in the EEN group and 5 days in the LEN group. Both the incidence and severity of RS were markedly higher in the LEN group, and serum potassium, sodium, phosphorus and magnesium levels were significantly lower in the LEN group on the third day after EN initiation. These findings suggest that early EN initiation may help reduce the risk of RS in critically ill patients with COVID-19 and high nutritional risk.

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Key words: enteral nutrition, refeeding syndrome, corona virus disease 2019

Introduction

A period of >5 years has passed since the emergence of coronavirus disease 2019 (COVID-19), yet the world continues to grapple with its impact (1). Successive waves of infection led to case fatality rates as high as 15% in certain populations, with mortality estimates suggesting that the true toll may be significantly worse than this (2,3). The cause of this lethal disease is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its worldwide effect was classified as a pandemic by the World Health Organization in March 2020 (4). Viral transmission is via human-to-human bodily fluid contact (droplet and/or aerosol), and the incubation period can be as long as 14-28 days before symptoms develop (5). Quarantine has proven effective in protecting susceptible people and reducing transmission rate.

The initial symptoms of most COVID-19 infections are often non-specific, such as coughing and dyspnea, while ~20% of patients present with gastrointestinal (GI) symptoms within the first 2 days of infection (6). Current interventions focus on supportive therapies, and novel vaccines have proven effective at mitigating disease severity (7,8).

The synergistic association between infection and malnutrition has been established (9). As COVID-19 progresses, ~5% of patients who become critically ill require an intensive care unit (ICU) admission, and regulating nutritional balance in these patients is vitally important for supportive care (10). Clinical reports have shown that the severity of COVID-19 infection is compounded by nutritional variables, especially for patients with GI symptoms (4). In this context, related studies have also demonstrated that nutritional support is a promising treatment for patients with COVID-19 and high nutritional risks (11-14).

To facilitate generalization of nutritional interventions, the president of the American Society for Parenteral and Enteral Nutrition (ASPEN) proposed a focused review of current clinical nutrition practices, including nutrition assessment, processing steps, monitoring and reassessment (15). The main points included: i) Early EN initiation, within 24-36 h of ICU admission or 12 h of intubation; ii) monitoring and reassessing patients during the EN/PN regimens; and iii) early EN may not be preferential in a subset of patients with GI symptoms; PN needing to be used early instead. Several malnutrition screening tools, such as Nutrition Risk Screen-2002 (NRS-2002), Global Leadership Initiative on Malnutrition (GLIM) (13,16,17), have gained widespread acceptance in recent years, largely due to their clinical practicality. These tools typically incorporate common clinical variables such as weight loss, body mass index (BMI), fat-free mass indices (FFMI) and signs of eating difficulties (such as appetite loss or reduced intake). The present study included BMI and FFMI for nutritional evaluation since their acquisitions were easy to access.

Recent studies on nutritional timing in ICU patients with COVID-19 found mixed outcomes regarding early versus delayed support. Some have reported that early enteral nutrition (EN) (within 24-48 h) can lead to reduced mortality and ICU stay, while others report equivocal findings with no clear advantage from early or delayed support, and they do not raise any concerns about tolerance during the acute phase (15-21).

Following ICU admission, EN could be started early as an effective way to improve nutritional status through nasogastric tube, even while patients are in a prone position (12). However, after EN initiation, refeeding syndrome (RS) can occur in patients who have been undernourished for a substantial period of time, owing to the wide range of metabolic and electrolyte imbalances, impaired glucose tolerance and vitamin deficiency in these patients (22,23). In severe cases, it can even lead to organ failure and death. The current definition of RS is a decrease in either serum potassium, phosphorus or magnesium level within 5 days of the reintroduction of calories (22). Based on the degree of reduction in the levels of these nutrients, RS is classified as mild (10-20%), moderate (20-30%) or severe (>30% or organ dysfunction resulting from a decrease of any of the aforementioned electrolyte ions or thiamine-deficiency) (22). It is reasonable to speculate that a delay in nutritional support could exacerbate RS since the period of nutrient restriction would be prolonged. However, for most COVID-19 patients at high risk of malnutrition, nutritional support is initiated as early as possible. Once the starvation period is excluded as a contributing factor, the method of nutritional intervention remains the key determinant influencing RS incidence. As the preferred nutritional therapy for patients with COVID-19, EN requires careful timing, composition and monitoring of total daily intakes. However, it remains unclear whether the timing of EN initiation influences RS incidence or severity in critically ill patients with COVID-19. To address this, a retrospective study was conducted on patients with COVID-19 who were admitted to the ICU, comparing different EN initiation times to assess their impact on RS incidence.

Patients and methods

Study population. The present study included critically ill patients with established COVID-19 infection, confirmed by the standard reverse transcriptase-polymerase chain reaction method, who were admitted to Tongji Hospital (Wuhan, China) between January 1 and December 31, 2020. Severe cases met at least one of the following criteria: i) Shortness of breath (respiratory rate ≥30 breaths/min); ii) oxygen saturation ≤93% in resting state; iii) partial pressure of arterial oxygen/inspired oxygen concentration ≤300 mmHg; and iv) obvious progress of lesion size by >50% within 24-48 h, as determined by pulmonary imaging (24,25).

Study procedures. Nutritional support was given to severely ill patients at high nutritional risk, as defined by ASPEN criteria within 24-36 h of ICU admission (15). EN was the first line of nutrient support for most patients, while parenteral nutrition (PN) was administered if EN was contraindicated or insufficient. EN was supplied with complete nutritional formula, such as whole protein preparations or short peptide/amino acid-based preparations. PN was provided with nutrient mixtures, including carbohydrates, fats, proteins, vitamins and minerals. A previous study (26) showed that RS prevalence is significantly associated withNRS-2002 scores. According to NRS-2002 scoring (27), a total of 304 cases in Tongji Hospital scored ≥3 points, representing those with a high nutritional risk.

Nutritional support was administered as quickly as possible following admission to the hospital. Energy requirement was determined based on energy expenditure calculations from indirect calorimetry measurements for each patient. Target nutritional requirement ranges were 25-30 kcal/(kg/day) total calories, 1.5-2.0 g/(kg/day) total protein and 7.8-11.1 mmol/l blood glucose. After admission, EN was the preferred route of administration. However, for patients with digestive symptoms or elevated risk of aspiration, PN was administered within 24-48 h and gradually shifted to EN thereafter. Once the nutritional ranges were achieved using EN, PN was discontinued. In severe cases, EN was administered through a nasogastric tube. Patients in a prone position could also receive EN under the rationale of prophylaxis for aspiration. The mean initial rate of EN therapy was 20 ml/h, and gradually increased to 70-100 ml/h. The dosage of EN therapy increased from 500 ml/day to 1,000 ml/day. During EN administration, each patient's tolerance was evaluated by checking the gastric residual volume every 4 h. If the residual volume was >500 ml, or accompanied with severe nausea, vomiting, diarrhea or other symptoms, EN infusion would be slowed, paused or changed to another EN reagent. For all COVID-19 patients with malnutrition risk, EN support was preferred for those without contraindications. PN was only applied for those who were EN intolerant or insufficient response from EN. To minimize the risk of RS associated with PN, electrolyte levels were continuously monitored throughout PN administration to ensure they remained within relatively normal ranges prior to initiating EN.

During the nutritional support period, serum electrolytes were measured daily. If any electrolyte levels dropped below the following thresholds, sodium <130 mmol/l, potassium <3.5 mmol/l, phosphorus<0.96 mmol/l and magnesium <0.70 mmol/l, then the corresponding electrolytes would be replenished as needed and carefully monitored to ensure they remained within the normal range. Throughout the entire course of nutritional support, levels of thiamine and other essential vitamins (such as vitamins D and E) were continuously monitored and promptly supplemented when found to be deficient. RS in the present study was identified according to the ASPEN definition as any one, two or three electrolyte imbalances, hypophosphatemia, hypokalemia and/or hypomagnesemia, after starting EN. A time cut-off time of 3 days after nutritional support was selected, which was within 5 days of reintroduction of calories.

Data collection. All patients who received EN therapy in this study were classified into two groups based on EN initiation intervals. The early EN (EEN) group were those with an interval from admission to first EN therapy of ≤2 days and the late EN (LEN) group were those with an interval from admission to first EN therapy of ≥3 days.

To ensure adequate sample size in the power estimates, an odds ratio (OR) of 2 was assumed for the association between LEN and RS, with a significance level (α) of 0.05 (two-sided) and a statistical power (1-β) of 0.8. Based on these parameters (OR, α, 1-β), the calculated minimum required sample size was 280 participants (case group, n=140; control group, n=140). A total of 211 cases were included in the final analysis, owing to limitations in patient volume and implementing inclusion/exclusion criteria. The inclusion criteria were as follows: i) Severe COVID-19, ii) NRS-2002 scores ≥3 points, iii) receiving EN support, iv) age ≥18 years and v) no immunodeficiency or malignant diseases. Exclusion criteria were as follows: i) Mild or moderate COVID-19, ii) NRS-2002 scores <3 points, iii) not needing nutritional support, or only PN support, iv) age <18 years and v) presence of immunodeficiency or malignant diseases.

The requirement for informed consent was waived from Tongji Hospital as this was a retrospective analysis. Data on patient demographics, symptoms, underlying diseases and laboratory examinations were collected from electronic medical records. Some interventions that could potentially affect nutritional status and RS incidence [for example, mechanical ventilation and renal replacement therapy (RRT)], were also compared between the two groups. Inflammatory and biochemical markers, including serum albumin, globulin, pH and creatinine, were measured upon admission. Additionally, serum phosphorus, potassium and magnesium levels were assessed on admission and 3 days after EN initiation as aforementioned.

Outcome variables. The primary outcome of the present study was the incidence and degree of RS 3 days after EN initiation. Patients were defined as RS-positive if they experienced a decrease below the aforementioned thresholds in serum phosphorus, potassium or magnesium level 3 days after EN initiation. Secondary outcomes were 3-month overall survival rate, in-hospital length of stay, ICU length of stay, incidence of airway complications and GI intolerance. Airway complications were defined as any episode of vomiting, followed by desaturation and formation of a mucus plug. Subjects who required frequent sputum suction (>2 times/h) and had episodes of temporary desaturation caused by airway obstruction due to sputum were defined as having a mucus plug (21). GI intolerance was defined as the appearance of serious diarrhea, nausea, vomiting, abdominal discomfort or GI bleeding after EN, which required therapeutic intervention (28).

Statistical analysis. Descriptive data are presented as the mean ± standard deviation and were confirmed by Student's t-test or Mann-Whitney U test. Categorical variables are presented as percentages and analyzed by the χ^2 test or Fisher's exact test. The 6-month survival curve was plotted using the Kaplan-Meier method with the log-rank test for analysis. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated to analyze the potential predictors for RS. Independent risk factors for RS were determined using logistic regression. Variables with a P-value <0.2 in the univariate analysis were included in the multivariate analysis. P<0.05 was considered to indicate a statistically significant difference. To further decrease the type I error, Bonferroni's correction adjustment was applied if necessary. All statistical analyses and plotting were performed using SPSS 22.0 (IBM Corp.) and GraphPad Prism 6.0 (Dotmatics).

Results

Baseline patient demographics and clinical variables. A total of 413 consecutive hospitalized patients with severe symptoms of COVID-19 infection were evaluated at Tongji Hospital (Wuhan, China) between January 2020 and December 2020. Among them, 211 patients with high nutritional risk received EN support. Of these, 122 patients required electrolyte supplementation during the first 3 days of EN. Table I shows the key demographic and clinical characteristics of participants based on EN initiation intervals, with 125 patients (59.24%) assigned to the EEN group and 86 patients (40.76%) assigned to the LEN group. Patient selection and group assignment criteria are shown in Fig. 1.

The mean age of all patients was 64 years, ranging from 46 to 92 years, and 101 patients (47.87%) were male. General symptoms of COVID-19 included fever, cough and respiratory distress. The most common comorbidity was hypertension (58.77% of the entire cohort). Both mechanical ventilation and RRT, which may be confounders for nutrition consumption, were similar between the groups (P=0.4380 and P=0.1075, respectively). Daily mean calories and protein intake were also not significantly different between groups (P=0.5063 and P=0.7304, respectively), which excluded some confounding factors for RS incidence. The nutritional state, including weight, BMI, FFMI and NRS-2002 scores on admission, was comparable between the two groups (all P≥0.05). The only significant difference between the two groups was the mean time interval to EN therapy initiation, which at 2 days in the EEN group, was significantly lower than the interval of 5 days in the LEN group (P=0.0413).

Serum electrolytes and blood variables. Baseline laboratory results for all patients were collected on admission and again 3 days after EN initiation (Table II; Fig. 2). At time of admission, blood cell counts for leukocytes, neutrophils and lymphocytes were similar between the two groups (all P>0.05). Likewise, serum levels of albumin, globulin, pH and creatinine were also not significantly different between

Table I. Demographic characteristics of patients with coronavirus disease 2019 according to EN initiation.

Variables	All (n=211)	EEN (n=125)	LEN (n=86)	P-value
Age, years	64±1.4	64±1.5	64±1.3	0.6974
Male sex, n (%)	101 (47.87)	51 (40.80)	50 (58.14)	0.1473
Weight, kg	60±1.6	59±1.6	60±1.5	0.5847
Body mass index, kg/m^2	22±0.4	22±0.4	22±0.3	0.5698
Fat-free mass indices, kg/m^2	17±0.5	17±0.4	16±0.7	0.5022
APACHE II score[a]	22±0.5	22±0.6	23±0.5	0.7872
Symptoms, n (%)				
Fever	184 (87.20)	104 (83.20)	80 (93.02)	0.4383
Cough	174 (82.46)	99 (79.20)	75 (87.21)	0.0788
Respiratory distress	103 (48.82)	65 (52.00)	38 (44.19)	0.7431
Underlying diseases, n (%)				
Hypertension	124 (58.77)	73 (58.40)	51 (59.30)	0.9803
Diabetes mellitus	78 (36.97)	42 (33.60)	36 (41.86)	0.4555
Chronic cardiovascular disease	47 (22.27)	28 (22.40)	19 (22.09)	0.5838
Chronic respiratory disease	42 (19.91)	24 (19.20)	18 (20.93)	0.4125
Past history, n (%)				
Smoking	56 (26.54)	34 (27.20)	22 (25.58)	0.4449
Drinking	24 (11.37)	16 (12.80)	8 (9.30)	0.4535
Mechanical ventilation, n (%)	110 (52.13)	70 (56.00)	40 (46.51)	0.4380
Renal replacement therapy, n (%)	24 (11.37)	16 (12.80)	8 (9.30)	0.1075
Caloric intake, Kcal/day	1778±11.4	1773±14.3	1785±10.5	0.5063
Protein intake, g/day	115±1.2	115±1.1	114±1.1	0.7304
Electrolyte supplementation from days 1 to day 3, n (%)	132 (62.56)	77 (61.60)	55 (63.95)	0.3020
NRS-2002 score	4±0.1	4±0.2	4±0.1	0.3897
Time interval to EN, days	3±0.1	2±0.1	5±0.1	0.0413[b]

[a](48). [b]P<0.05. Data are presented as mean + SD unless otherwise stated. EN, enteral nutrition; EEN, early EN; LEN, late EN; NRS-2002, Nutrition Risk Screen-2002.

groups (all P>0.05). Both groups displayed similar electrolyte balance, all within the acceptable range (all P>0.05). At 3 days post-EN initiation, there was a significant reduction in potassium, sodium, phosphorus and magnesium levels in the LEN group compared with those in the EEN group (P=0.0071, P=0.0263, P=0.0373 and P=0.0164, respectively), with all of these electrolytes falling below the clinically acceptable range. In order to decrease the type I error incidence, Bonferroni's correction was applied. After adjustment, only the changes in serum potassium (P=0.0213) and magnesium (P=0.0492) levels at 3 days post-EN initiation remained statistically significant (Table II; Fig. S1).

Primary and secondary outcomes. RS incidence was significantly lower in the EEN group compared with that in the LEN group (27.20% vs. 60.47%, P=0.0440), with RS severity higher in the LEN group, since 63.46% of patients had 'moderate' RS compared with 41.18% in the EEN group (P=0.0236) (Table III). There were no significant differences in overall survival between the two groups at 3 months (P=0.4701) (Fig. 3). Notably, despite the similar mortality rates, in-hospital and ICU stay lengths were significantly lower in the EEN group (19.46±0.81 vs. 29.22±1.10, P<0.0001; and 17.16±1.04 vs. 22.39±1.50, P=0.0099, respectively). Moreover, the EEN group did not experience any significant increase in risk of airway complications or GI intolerance (P=0.0742 and P=0.3392, respectively) (Table III).

Prediction of RS incidence. ROC curves and their associated AUCs for both the EEN and LEN groups are shown in Fig. 4 and Table IV, respectively. AUC values for most parameters, including age, sex, and serum electrolytes at admission, were within the range of 0.447-0.573 (all P>0.05), which could not effectively predict RS incidence. However, the EN initiation AUC was 0.667 (P=0.022), indicating a reasonable predictive value for this variable.

Logistic regression analysis for RS incidence. Potential independent risk factors for RS incidence were analyzed using logistical regression. Univariate analysis revealed that EN initiation time was associated with RS (P<0.001). Using a P-value of <0.2 as a cut-off, age, EN initiation, hypertension, and chronic respiratory disease were included in the multivariate analysis. It was determined that RS incidence was 6.530-fold higher in the LEN group compared with that in the EEN group (OR, 6.530; confidence interval, 2.895-14.727;

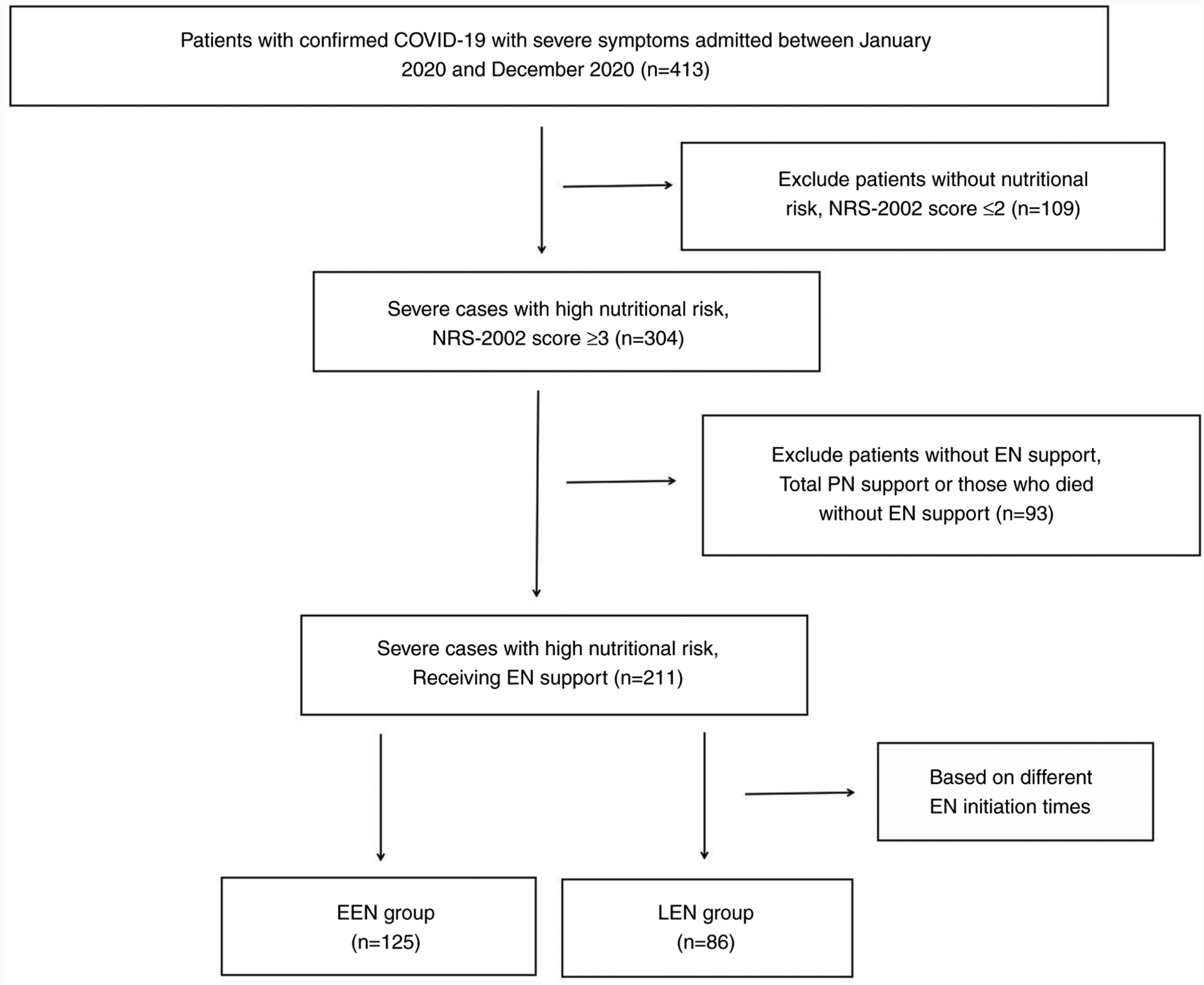

Figure 1. Flow diagram of participant selection procedure. COVID-19, coronavirus disease 2019; NRS-2002, Nutrition Risk Screen-2002; PN, parenteral nutrition; EN, enteral nutrition; EEN, early EN; LEN, late EN.

P<0.001), suggesting EN initiation as an independent predictor for RS (Table V).

Discussion

COVID-19 has brought immeasurable adverse health effects to the world, including nutritional deficiency, which can affect as many as 30% of infected patients, according to most reports. Moreover, if such patients have protein deficiencies or electrolyte imbalance, their mortality rate will further increase (9). There are several ways in which COVID-19 can adversely impact nutrition, digestion and absorption. First, it has been shown that SARS-CoV-2 binds human angiotensin-converting enzyme 2 (ACE-2) receptor on hepatocytes derived from bile duct epithelial cells, thus causing liver tissue injury via ACE-2 upregulation (6). Second, ACE-2 receptors are also expressed on ileum and colon enterocytes, and proliferation of these cells caused by viral-mediated ACE-2 activation can disrupt the intestinal flora (5). Finally, inflammatory responses to the virus can induce dysbiosis and GI disturbance, especially diarrhea (4). Several studies have identified the association between nutritional risk and mortality in critically ill patients with COVID-19. Zhao *et al* (28) reported that critical COVID-19 patients had significantly higher NRS-2002 scores, leading to longer hospital stays and a higher risk of mortality. Furthermore, a report by Li *et al* (16) confirmed the prevalence of malnutrition in elderly patients with COVID-19 in Wuhan, China. The nutritional status of the participants was determined by a clinical nutritionist, and the mean NRS-2002 score was 3, indicating a high risk of malnutrition and the need for nutritional support (17).

The therapeutic benefits of nutritional support to reduce the severity of COVID-19 illness has been described by several recent reviews (15,18-21). Specifically, experts from ASPEN extrapolated the results of previous studies and recommended initiating nutritional support within 24-36 h of admission for critically ill patients with COVID-19 (15). The expert consensus from the European Society for Clinical Nutrition and Metabolism suggests that nutritional support could be initiated within 1-2 days for patients with COVID-19 undergoing mechanical ventilation therapy (18). Recent reports have further demonstrated the benefits of early nutritional support in ICU patients with COVID-19. For instance, Haines *et al* (19) found that early nutrition in

Table II. Laboratory examination of patients with coronavirus disease 2019 according to EN initiation.

A, Admission

Variables	All (n=211)	EEN (n=125)	LEN (n=86)	P-value	P-value (Bonferroni's correction)
Leukocytes (x10^9/l)	8.874±0.7250	8.901±0.7324	8.846±0.6977	0.5470	/
Neutrophils (x10^9/l)	7.512±0.7158	7.520±0.7443	7.507±0.6869	0.6984	/
Lymphocytes (x10^9/l)	0.855±0.0715	0.822±0.0794	0.881±0.0637	0.4631	/
Albumin, g/l	32.19±0.6886	32.13±0.7904	32.24±0.5867	0.1796	/
Globulin, g/l	35.03±0.7327	34.98±0.8993	35.07±0.5642	0.0792	/
pH	7.401±0.0039	7.401±0.0043	7.402±0.0034	0.7953	/
Creatinine, μmol/l	130.5±5.2535	135.8±5.8310	124.4±4.6760	0.1253	/
Potassium, mmol/l	4.372±0.0803	4.403±0.0834	4.349±0.0771	0.7103	/
Sodium, mmol/l	141.5±0.7088	142.0±0.9232	141.1±0.6445	0.0684	/
Phosphorus, mmol/l	1.032±0.0448	1.039±0.0482	1.027±0.0394	0.9099	/
Magnesium, mmol/l	0.899±0.0273	0.928±0.0299	0.882±0.0216	0.5255	/

B, 3 days after EN initiation

Variables	All (n=211)	EEN (n=125)	LEN (n=86)	P-value	P-value (Bonferroni's correction)
Potassium, mmol/l	4.029±0.0889	4.540±0.1093	3.432±0.0683	0.0071[a]	0.0213[a]
Sodium, mmol/l	139.8±0.5276	143.6±0.5226	134.8±0.5287	0.0263[a]	0.0789
Phosphorus, mmol/l	0.944±0.0913	1.114±0.1023	0.838±0.0802	0.0373[a]	0.1119
Magnesium, mmol/l	0.789±0.0257	0.938 ± 0.0337	0.691 ± 0.0181	0.0164[a]	0.0492[a]

[a]P<0.05. EN, enteral nutrition; EEN, early EN; LEN, late EN.

Table III. Outcomes of subjects with coronavirus disease 2019 in the groups receiving early versus late EN.

Outcomes	All (n=211)	EEN (n=125)	LEN (n=86)	P-value
Refeeding syndrome, n (%)	86 (40.76)	34 (27.20)	52 (60.47)	0.0440[a]
Mild	39 (45.35)	20 (58.82)	19 (36.54)	0.0236[a]
Moderate	47 (54.65)	14 (41.18)	33 (63.46)	
3-Month mortality, n (%)	106 (50.24)	69 (55.20)	37 (43.02)	0.4701
In-hospital stay length, days	24.95±0.964	19.46±0.813	29.22±1.095	<0.0001[a]
ICU stay length, days	20.23±1.277	17.16±1.037	22.39±1.495	0.0099[a]
Airway complications, n (%)	82 (38.86)	54 (43.20)	28 (32.56)	0.0742
GI intolerance, n (%)	80 (37.91)	44 (35.20)	36 (41.86)	0.3392

[a]P<0.05. EN, enteral nutrition; EEN, early EN; LEN, late EN; ICU, Intensive Care Unit; GI, gastrointestinal.

mechanically ventilated patients was associated with faster weaning from mechanical ventilation and decreased length of stay in the ICU and hospital overall. A meta-analysis by Ojo *et al* (20) further concluded that early nutritional intervention significantly reduced mortality risk among critically ill patients with COVID-19 (20). Additionally, Yuan *et al* (21) reported that EEN was the preferred method of support for elderly patients with common-type COVID-19 (21). Some studies also suggest that non-critically ill patients would benefit from early nutritional supplementation, particularly increased protein and calorie intake through oral supplements (29-31). Carbohydrates, lipids, amino acid supplements, vitamins and minerals have been shown to reduce the risk of COVID-19 infection and death (30). For example, vitamin C supplementation may reduce the susceptibility to lower respiratory tract infections, while vitamin D could induce cathelicidins and defensins to inhibit the viral replication rate (31).

Table IV. ROC curve of risk model for refeeding syndrome with coronavirus disease 2019.

				Asymptotic 95% confidence interval	
Variables	AUROC	Standard error	P-value	Lower bound	Upper bound
Age	0.573	0.072	0.316	0.431	0.715
Sex	0.530	0.075	0.676	0.383	0.677
EN	0.667	0.072	0.022[a]	0.526	0.808
Admission					
Potassium	0.486	0.072	0.844	0.345	0.627
Sodium	0.447	0.071	0.470	0.308	0.587
Phosphorus	0.472	0.074	0.698	0.328	0.616
Magnesium	0.470	0.072	0.685	0.330	0.611

[a]P<0.05. ROC, receiver operating characteristic; EN, enteral nutrition; AUROC, area under receiver operating characteristic curve.

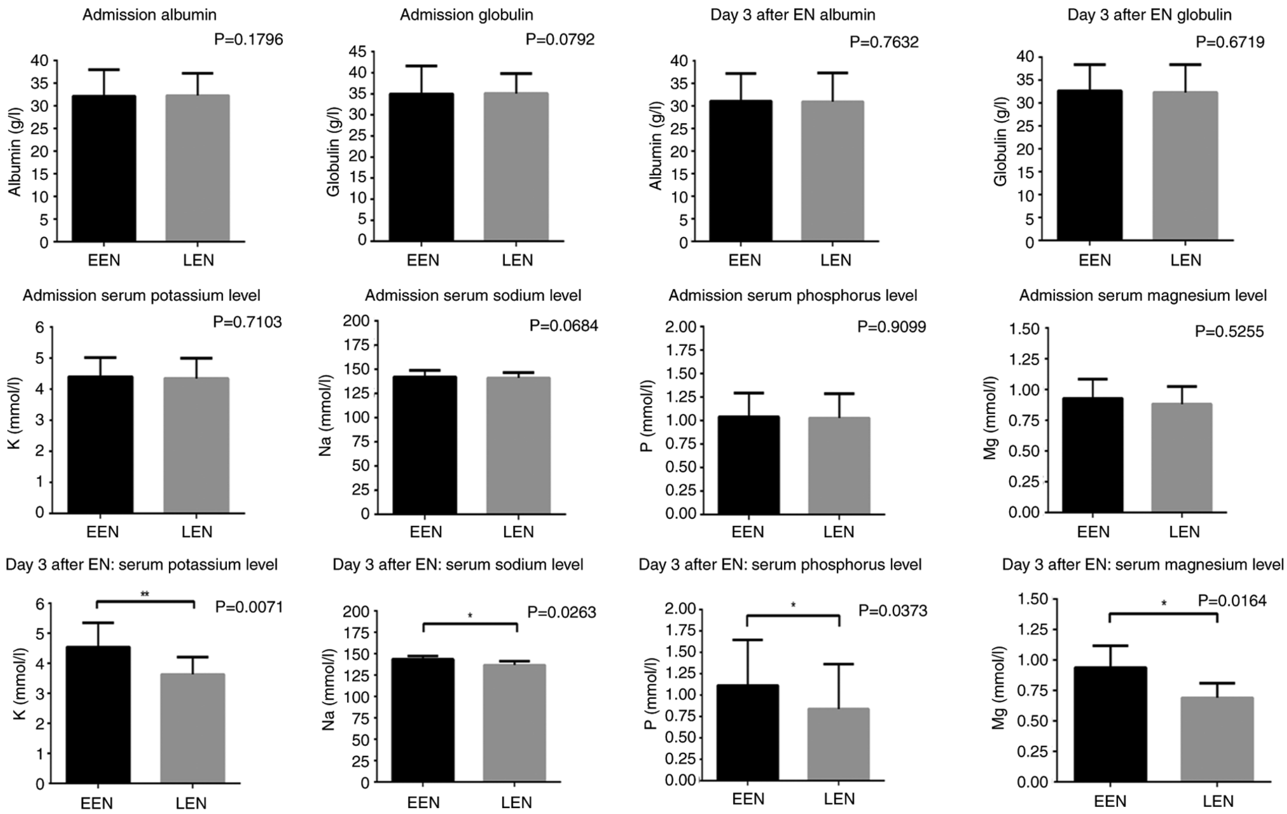

Figure 2. Laboratory examinations on admission and 3 days after EN initiation. *P<0.05 and **P<0.05. EN, enteral nutrition; EEN, early EN; LEN, late EN.

Although EN and PN are the most commonly employed routes of administration for nutritional support, most clinicians prefer EN (15). Theoretical benefits of EN include the preservation of integral mucosal architecture, gut-associated lymphoid tissue and hepatic immune function. EN may also reduce inflammatory responses during nutritional input and prevent antigen leak from the gut, as previously shown (32). A practical nutritional guideline for patients with COVID-19, published by Thibault *et al* (12), states that EN delivered within 48 h of ICU admission should be the first-line intervention, while PN should be prescribed if EN is contraindicated or insufficient (12). Adequate early EN support has contributed to improved clinical outcomes in mechanically ventilated patients with COVID-19 (33). For these reasons, EN support was applied for the most severe COVID-19 cases in Tongji Hospital during the study period. Patients in the EEN group received EN support within 2 days of admission and gradually transitioned to oral nutrition after that. For patients with digestive symptoms or those at high risk of aspiration, PN support was initiated within 24-48 h and gradually transitioned to EN. In the present cohort, PN was applied to all patients in the LEN group within 2 days of admission. Although previous observations have shown that nutritional supplements administered at an early stage are important for enhancing host resistance to

Table V. Univariate and multivariate analysis of risk factors related to refeeding syndrome.

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex (female vs. male)	1.435 (0.705-2.920)	0.319		
Age	1.019 (0.987-1.053)	0.145	1.013 (0.975-1.053)	0.497
EN (LEN vs. EEN)	6.327 (2.863-13.982)	<0.001[a]	6.530 (2.895-14.727)	<0.001[a]
Weight	0.991 (0.964-1.020)	0.556		
Body mass index	1.012 (0.899-1.139)	0.843		
APACHE II score	1.013 (0.931-1.102)	0.766		
Smoking	0.263 (0.029-2.419)	0.238		
Drinking	0.871 (0.223-3.409)	0.843		
Hypertension	1.669 (0.824-3.377)	0.115	1.781 (0.792-4.001)	0.163
Diabetes mellitus	1.500 (0.637-3.531)	0.353		
Chronic cardiovascular disease	0.769 (0.287-2.063)	0.602		
Chronic respiratory disease	2.333 (0.557-9.777)	0.146	2.182 (0.454-10.494)	0.330
Mechanical ventilation	1.487 (0.735-3.009)	0.269		
Calories intake	0.999 (0.995-1.003)	0.550		
Protein intake	0.989 (0.952-1.028)	0.574		
Admission				
Potassium	1.350 (0.720-2.529)	0.350		
Sodium	0.969 (0.911-1.031)	0.317		
Phosphorus	0.453 (0.062-3.318)	0.436		
Magnesium	0.289 (0.010-8.266)	0.468		

[a]P<0.05. EN, enteral nutrition; EEN, early EN; LEN, late EN; OR, odds ratio; CI, confidence interval.

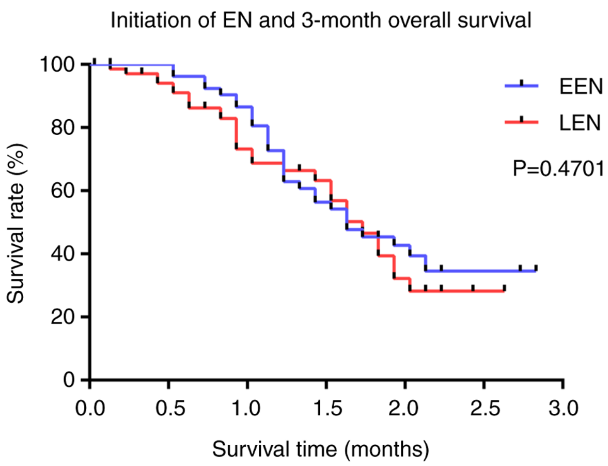

Figure 3. Kaplan-Meier survival curve for 3-month overall survival. EN, enteral nutrition; EEN, early EN; LEN, late EN.

virus infection, there is still no consensus on the best time to initiate EN (34). For patients with severe COVID-19 and high nutritional risk, it is difficult to avoid RS after EN support, even with adequate daily electrolyte supplementation (35). However, whether there is an association between EN initiation time and the incidence of RS is still unclear.

RS encompasses a range of metabolic and electrolyte imbalances that occur due to the reintroduction or increased provision of calories after a period of caloric restriction (22). All patients included in the study had a reduction of caloric intake with high nutritional risk upon admission, therefore were at higher risk of RS. To prevent RS in these patients, the strategy was to provide essential electrolyte supplementation if they were below a daily threshold. Furthermore, some measures were also taken to ensure that proper nutrition and electrolytes were within a normal range during the PN period, in order to ensure a smooth transition to EN support. Since RS often occurs within 5 days of reintroduction of calories, serum electrolytes were monitored 3 days after initiating EN to identify RS incidence and degree of severity. A time cut-off of 3 days was chosen since it was the median for peak incidence of the RS. The relative electrolytes were significantly changed from the start of monitoring to the end. Hypophosphatemia is often considered the hallmark of this syndrome owing to the rapid egress of phosphorus ions from the intravascular to intracellular space after EN initiation (36). Intracellular phosphate plays a key role in adenosine triphosphate (ATP) production and transfer within cells, and increased consumption of phosphate during refeeding can indirectly lead to reduced ATP and 2,3-diphosphoglycerate generation due to enhanced production of phosphorylated intermediates, thereby causing impairments in cardiac and respiratory functions (37). Hypokalemia and hypomagnesemia are also of equal importance. Decreased serum potassium causes an imbalance in the electrochemical membrane potential and disturbs cardiac

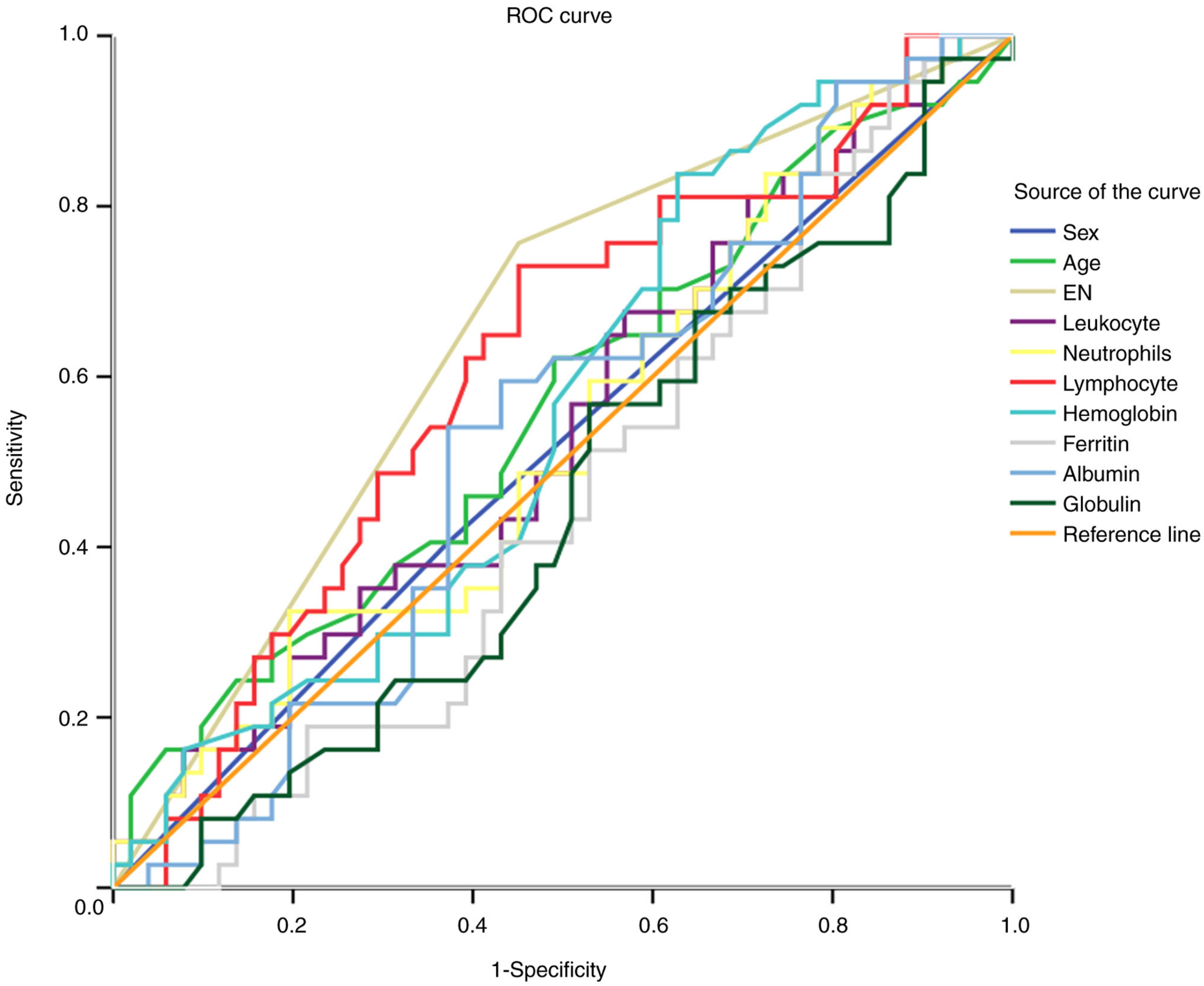

Figure 4. ROC curves for predicting the refeeding syndrome incidence. ROC, receiver operating characteristic; EN, enteral nutrition.

electromechanical function and nerve impulses, resulting in abnormal cardiac rhythm and neurotransmitter release (38). Hypokalemia also causes paralysis in the neuromuscular junction (39). Serum magnesium is essential for activating the sodium/potassium ATP-pump (Na^+/K^+-ATPase), and magnesium deficiency could aggravate potassium loss in cardiomyocytes, reflected by lengthening of the PR and QT intervals in an electrocardiogram (ECG) and widening of the QRS complex, all of which leads to an increased risk of tachyarrhythmias (40).

In the present study, serum electrolyte and blood cell values upon hospital admission were similar between the two groups and were within the normal ranges. Although measures were taken to maintain electrolyte levels within normal limits before transitioning to EN, the potential risk of RS could not be entirely avoided. There were no differences in daily calories or protein intake, and nutritional content and composition were similar between groups. BMI, as a commonly used anthropometric index applied in clinical and research settings, has well-recognized limitations when used as a standalone marker of nutritional status. BMI alone does not accurately reflect muscle mass and may obscure underlying sarcopenia or malnutrition, especially in older adults or critically ill patients (10,16). FFMI was therefore included as another nutritional assessment indicator for the present study. Certain confounding factors, such as mechanical ventilation and RRT, which can potentially affect electrolyte balances, were also excluded, since these interventions were equally administered in both groups. At 3 days post-EN initiation, the serum electrolyte levels were significantly lower in the LEN group compared with those in the EEN group. Moreover, each of these electrolytes was below clinically acceptable levels in the LEN group, suggesting that delayed EN initiation may have adverse effects on homeostasis. A significantly higher incidence and severity of RS was also observed in the LEN group. It was reasoned that 2 days was the appropriate time interval to distinguish early from late EN initiation, as studies show that intestinal dysbacteriosis occurs within 48 h of discontinuing normal gut nutritional support. Later initiation of EN further impairs integral mucosal architecture and increases the risk of bacterial translocation (41). Delayed EN support is a known risk factor for RS. Notably, the ROC analysis in the present study found that the AUC for EN was 0.667, which is favorable for RS prediction. Additionally, logistical regression demonstrated that the risk of RS was 4-fold higher in the LEN group compared with that in the EEN group.

Two important physiological processes occur after initiating EN. Increased insulin secretion drives glucose into cells, which results in increased uptake of serum phosphorus, potassium, magnesium, calcium and thiamine. This causes Na^{+}/K^{+}-ATPase to increase active exchange of these ions across the plasma membrane (Na^{+} pumped out and K^{+} pumped into the cell). In turn, cellular uptake of serum phosphorus and magnesium is further increased (42). In light of the aforementioned two effects, early nutritional support is beneficial for regulating the body's ability to tolerate changes in the internal environment following initiation, thereby reducing the likelihood of RS.

The association between EN initiation and mortality in other respiratory diseases has been widely investigated. Zhong *et al* (41) (2017) found that early EN support could improve nutritional status, decrease blood glucose fluctuations and further improve the 28-day mortality rate in patients with acute respiratory distress syndrome (ARDS), a common complication of severe COVID-19. Subsequently, Yan *et al* (43) (2018) showed a similar result wherein early EN support reduced the incidence of infection, improved lung function, and reduced the duration of mechanical ventilation and length of ICU stay in patients with ARDS. By contrast, Peterson *et al* (44) (2017) suggested that early administration of high-calorie support was associated with increased mortality in patients with ARDS, while initiating support after day 8 decreased the risk. An important finding in the present study was that EEN support was significantly associated with decreased length of stay in the hospital and in the ICU, without affecting the 3-month overall survival rate. During the course of treatments, all patients with severe COVID-19 receive similar therapies, including respiratory and circulatory monitoring, electrolyte supplementation and use of glucocorticoids. After excluding these treatment confounding factors, EEN support showed no effect on long-term mortality. The patients in the LEN group had worse GI symptoms, characterized by severe nausea, vomiting and diarrhea. Given that it takes some time to transition from PN to EN to ensure EN efficacy and safety, it is not unexpected to see that the patients in the LEN group took a longer time for proper GI function, or that they required longer stays in the ICU and in the hospital.

Finally, to evaluate the safety of early EN initiation in the present study, the incidence rates of airway complications and GI intolerance were evaluated. According to an earlier report, nearly 20% of critically ill patients who received EN during non-invasive positive pressure ventilation developed at least one adverse event, including pneumonia and progressive respiratory failure (43). Efforts to provide early EN can be further impaired by GI intolerance and bleeding (44). In the present study, the incidence of airway complications and GI intolerance were similar between the two groups, in part owing to the excellent quality of patient care and regular monitoring provided by the hospital staff. Collectively, these findings indicate that early EN can be safely initiated for patients with severe COVID-19 and high nutritional risk.

The present study has several limitations. First, only the NRS-2002 clinical scoring tool was used, which, although validated for identifying malnutrition, does not provide a formal diagnosis or severity grading. A more recent and globally endorsed tool named the GLIM criteria offers a standardized diagnostic framework based on etiological and phenotypic criterion (45), but this was not applied and measured in the present study, since we could not obtain comprehensive data regarding the participants' weight losses over the previous 6-month period. Its inclusion in future studies could improve diagnostic consistency and enable severity classification. Second, the retrospective single-center design may introduce selection bias and limit the generalizability of the present findings. The observed association between EN interval timing and RS incidence reflects association, not causation. Moreover, the study failed to reach a sufficient calculated sample size owing to limitations in patient volume and implementing inclusion/exclusion criteria, and as a result, adjustment with Bonferroni's correction was only applied to a significantly certain criterion (electrolytes), since it was the most important variable for RS incidence. Furthermore, due to limited sample sizes within certain subgroups, stratified analyses were not performed in the current study, and this may bring about poor stability for the results. To better address the issue of insufficient sample size, a large, prospective study is needed to confirm these findings, provided that patient safety is ensured. Third, the present study population was limited to patients with severe COVID-19 with NRS scores ≥ 3, excluding those with milder symptoms or lower nutritional risk. As a result, the potential benefit of early EN in less severe cases remains unclear. Fourth, there was no way to determine how long participants had been undernourished prior to admission, despite all presenting with high nutritional risk. Additionally, to meet baseline caloric needs, patients in the LEN group received PN before EN. This introduced a key limitation, as PN is a known risk factor for RS owing to its high carbohydrate content and potential for electrolyte shifts. Therefore, the association between delayed EN and increased RS incidence may be confounded by prior PN exposure rather than EN timing alone. The present study design did not permit full adjustment for this variable, and future studies should control for PN use either through stratification or multivariable analysis or compare early PN and EN cohorts separately to reduce this bias. The lack of propensity score matching or covariate adjustment must all be acknowledged, as this may have introduced bias. Causal inference would be strengthened with larger studies that incorporate these methods. It is also plausible that routine use of thiamine, multivitamins and electrolyte management among each patient in their daily lives may have reduced RS risk, although the extent of this effect could not be fully assessed in the present retrospective analysis. Lastly, only 3-month survival rate was recorded in this cohort, and it may not have been sufficient to adequately differentiate mortality risk between the EEN and LEN groups. Longer-term outcomes should be evaluated in future studies.

In conclusion, EN initiation within 2 days after hospital admission was associated with reduced RS incidence and decreased length of stay in the hospital and in the ICU, although this therapy had no effect on overall survival rate at 3 months post-infection. These findings suggest that early initiation of EN support is recommended to reduce RS incidence for severely ill patients with COVID-19 and high nutritional risk if they do not have EN contraindications.

Acknowledgements

Not applicable.

Funding

This study was supported by the COVID-19 Rapid Response Research Project of Huazhong University of Science and Technology (grant no. 2020kfyXGYJ049).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LX contributed to the conception and design of the research. XR contributed to the acquisition and analysis of the data. LX and XR contributed to the interpretation of the data. SL contributed to the statistical analysis. XR and SL confirm the authenticity of all the raw data. SL agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LX and SL drafted the manuscript and revised it critically for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was a retrospective study, so the requirement for informed consent was waived by Tongji Hospital Ethics Committee (Wuhan, China). The requirement for ethical approval was also waived by the ethics committee, and clinical research related to the severe corona virus disease 2019 was strongly encouraged by Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang J, Yu M, Tong S, Liu LY and Tang LV: Predictive factors for disease progression in hospitalized patients with coronavirus disease 2019 in Wuhan, China. J Clin Virol 127: 104392, 2020.
2. Cambon L, Bergeron H, Castel P, Ridde V and Alla F: When the worldwide response to the COVID-19 pandemic is done without health promotion. Glob Health Promot 28: 3-6, 2021.
3. McDermott KT, Perry M, Linden W, Croft R, Wolff R and Kleijnen J: The quality of COVID-19 systematic reviews during the coronavirus 2019 pandemic: An exploratory comparison. Syst Rev 13: 126, 2024.
4. Aguila EJT, Cua IHY, Fontanilla JAC, Yabut VLM and Causing MFP: Gastrointestinal manifestations of COVID-19: Impact on nutrition practices. Nutr Clin Pract 35: 800-805, 2020.
5. Aguila EJT, Cua IHY, Dumagpi JEL, Francisco CPD, Raymundo NTV, Sy-Janairo MLL, Cabral-Prodigalidad PAI and Lontok MAD: COVID-19 and its effects on the digestive system and endoscopy practice. JGH Open 4: 324-331, 2020.
6. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, *et al*: Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. Am J Gastroenterol 115: 766, 2020.
7. Haq EU, Yu J and Guo J: Frontiers in the COVID-19 vaccines development. Exp Hematol Oncol 9: 24, 2020.
8. Kumar V, Srinivasan V and Kumara S: Smart vaccine manufacturing using vovel biotechnology platforms: A study during COVID-19. J Comput Inf Sci Eng 22: 040903, 2022.
9. Hakeem R and Sheikh MA: Beyond transmission: Dire need for integration of nutrition interventions in COVID-19 pandemic-response strategies in Developing Countries like Pakistan. Pak J Med Sci 36(COVID19-S4): S85-S89, 2020.
10. Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M and Mcclave SA: Nutrition therapy in critically Ill patients with coronavirus disease 2019. JPEN J Parenter Enteral Nutr 44: 1174-1184, 2020.
11. Chapple LS, Fetterplace K, Asrani V, Burrell A, Cheng AC, Collins P, Doola R, Ferrie S, Marshall AP and Ridley EJ: Nutrition management for critically and acutely unwell hospitalised patients with coronavirus disease 2019 (COVID-19) in Australia and New Zealand. Aust Crit Care 33: 399-406, 2020.
12. Thibault R, Seguin P, Tamion F, Pichard C and Singer P: Nutrition of the COVID-19 patient in the intensive care unit (ICU): A practical guidance. Crit Care 24: 447, 2020.
13. Stachowska E, Folwarski M, Jamioł-Milc D, Maciejewska D and Skonieczna-Żydecka K: Nutritional support in coronavirus 2019 disease. Medicina (Kaunas) 56: 289, 2020.
14. Zhang L and Liu Y: Potential interventions for novel coronavirus in China: A systematic review. J Med Virol 92: 479-490, 2020.
15. Wells Mulherin D, Walker R, Holcombe B and Guenter P: ASPEN report on nutrition support practice processes with COVID-19: The first response. Nutr Clin Pract 35: 783-791, 2020.
16. Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L and Duan J: Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. Eur J Clin Nutr 74: 871-875, 2020.
17. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barazzoni R, Blaauw R, Coats AJS, *et al*: GLIM criteria for the diagnosis of malnutrition-A consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle 10: 207-217, 2019.
18. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, Pirlich M and Singer P; endorsed by the ESPEN Council: ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr 39: 1631-1638, 2020.
19. Haines K, Parker V, Ohnuma T, Krishnamoorthy V, Raghunathan K, Sulo S, Kerr KW, Besecker BY, Cassady BA and Wischmeyer PE: Role of early enteral nutrition in mechanically ventilated COVID-19 patients. Crit Care Explor 4: e0683, 2022.
20. Ojo O, Ojo OO, Feng Q, Boateng J, Wang X, Brooke J and Adegboye ARA: The effects of enteral nutrition in critically Ill patients with COVID-19: A systematic review and meta-analysis. Nutrients 14: 1120, 2022.
21. Yuan J, Guan Y, Zhao Z, Shen J, Tan D, Zhao F, Ge L, Xie R and Li T: Enteral nutrition therapy for elderly patients with common-type COVID-19, a retrospective study based on medical records. Int Health 17: 678-684, 2025.
22. Da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW, Cober MP, Evans DC, Greaves JR, Gura KM, *et al*: ASPEN consensus recommendations for refeeding syndrome. Nutr Clin Pract 35: 178-195, 2020.
23. Meira APC, Santos COD, Lucho CLC, Kasmirscki C and Silva FM: Refeeding syndrome in patients receiving parenteral nutrition is not associated to mortality or length of hospital stay: A retrospective observational study. Nutr Clin Pract 36: 673-678, 2021.
24. Zhu Z, Cai T, Fan L, Lou K, Hua X, Huang Z and Gao G: Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis 95: 332-339, 2020.
25. Liu F, Li L, Xu M, Wu J, Luo D, Zhu Y, Li B, Song X and Zhou X: Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol 127: 104370, 2020.

26. Pourhassan M, Cuvelier I, Gehrke I, Marburger C, Modreker MK, Volkert D, Willschrei HP and Wirth R: Risk factors of refeeding syndrome in malnourished older hospitalized patients. Clin Nutr 37: 1354-1359, 2018.
27. Kogo M, Nagata K, Morimoto T, Ito J, Sato Y, Teraoka S, Fujimoto D, Nakagawa A, Otsuka K and Tomii K: Enteral nutrition is a risk factor for airway complications in subjects undergoing noninvasive ventilation for acute respiratory failure. Resp Care 62: 459-467, 2017.
28. Zhao X, Li Y, Ge Y, Shi Y, Lv P, Zhang J, Fu G, Zhou Y, Jiang K, Lin N, *et al*: Evaluation of nutrition risk and its association with mortality risk in severely and critically Ill COVID-19 patients. JPEN J Parenter Enteral Nutr 45: 32-42, 2021.
29. Caccialanza R, Laviano A, Lobascio F, Montagna E, Bruno R, Ludovisi S, Corsico AG, Di Sabatino A, Belliato M, Calvi M, *et al*: Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. Nutrition 74: 110835, 2020.
30. Grant WB, Lahore H, Mcdonnell SL, Baggerly CA, French CB, Aliano JL and Bhattoa HP: Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12: 988, 2020.
31. Rozga M, Cheng FW, Moloney L and Handu D: Effects of micronutrients or conditional amino acids on COVID-19-related outcomes: An evidence analysis center scoping review. J Acad Nutr Diet 121: 1354-1363, 2021.
32. Ohbe H, Jo T, Matsui H, Fushimi K and Yasunaga H: Early enteral nutrition in patients undergoing sustained neuromuscular blockade: A propensity-matched analysis using a nationwide inpatient database. Crit Care Med 47: 1072-1080, 2019.
33. Melchers M, Hubertine Hermans AJ, Hulsen SB, Kehinde Kouw IW and Hubert van Zanten AR: Individualised energy and protein targets achieved during intensive care admission are associated with lower mortality in mechanically ventilated COVID-19 patients: The COFEED-19 study. Clin Nutr 42: 2496-2492, 2023.
34. Seres DS, Valcarcel M and Guillaume A: Advantages of enteral nutrition over parenteral nutrition. Therap Adv Gastroenterol 6: 157-167, 2013.
35. Alexander J, Tinkov A, Strand TA, Alehagen U, Skalny A and Aaseth J: Early nutritional interventions with zinc, selenium and vitamin D for raising anti-viral resistance against progressive COVID-19. Nutrients 12: 2358, 2020.
36. Ribeiro AC, Dock-Nascimento DB, Silva JM Jr, Caporossi C and Aguilar-Nascimento JE. Hypophosphatemia and risk of refeeding syndrome in critically ill patients before and after nutritional therapy. Rev Assoc Med Bras (1992) 66: 1241-1246, 2020.
37. Ponzo V, Pellegrini M, Cioffi I, Scaglione L and Bo S: The refeeding syndrome: A neglected but potentially serious condition for inpatients. A narrative review. Intern Emerg Med 16: 49-60, 2021.
38. Matthews-Rensch K, Capra S and Palmer M: Systematic review of energy initiation rates and refeeding syndrome outcomes. Nutr Clin Pract 36: 153-168, 2021.
39. De Silva A and Nightingale JMD: Refeeding syndrome: Physiological background and practical management. Frontline Gastroenterol 11: 404-409, 2019.
40. Yoshida M, Izawa J, Wakatake H, Saito H, Kawabata C, Matsushima S, Suzuki A, Nagatomi A, Yoshida T, Masui Y and Fujitani S: Mortality associated with new risk classification of developing refeeding syndrome in critically ill patients A cohort study. Clin Nutr 40: 1207-1213, 2021.
41. Zhong C, Ji C, Dai Z, Fu K, Wen X and Pan H: Effect of early enteral nutrition standardized treatment on blood glucose and prognosis in acute respiratory distress syndrome patients with mechanical ventilation. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 29: 1133-1137, 2017 (In Chinese).
42. Ghaddar R, Chartrand J, Benomar A, Jamoulle O, Taddeo D, Frappier JY and Stheneur C: Excessive laboratory monitoring to prevent adolescent's refeeding syndrome: Opportunities for enhancement. Eat Weight Disord 25: 1021-1027, 2020.
43. Guo Y, Cheng J and Li Y: Influence of enteral nutrition initiation timing on curative effect and prognosis of acute respiratory distress syndrome patients with mechanical ventilation. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 30: 573-577, 2018.
44. Peterson SJ, Lateef OB, Freels S, Mckeever L, Fantuzzi G and Braunschweig CA: Early exposure to recommended calorie delivery in the intensive care unit is associated with increased mortality in patients with acute respiratory distress syndrome. JPEN J Parenter Enteral Nutr 42: 739-747, 2018.
45. Yildirim M, Halacli B, Yuce D, Gunegul Y, Ersoy EO and Topeli A: Assessment of admission COVID-19 associated hyperinflammation syndrome score in critically-III COVID-19 patients. J Intensive Care Med 38: 70-77, 2023.