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Review

Review

Gut, metabolism and nutritional Support for COVID-19: Experiences from China

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Abstract

There is little research that focuses on the relationship between the gut, metabolism, nutritional support and COVID-19. As a group of Chinese physicians, nutritionists and scientists working on the frontline treating COVID-19 patients, we aim to integrate our experiences and the current clinical evidence to address this pressing issue in this article. Based on our clinical observations and available evidence, we recommend the following practice. Firstly, the Nutritional Risk Screening 2002 tool should be used routinely and periodically; for patients with a score $\geq$3, oral nutritional supplements should be given immediately. Secondly, for patients receiving the antiviral agents lopinavir/ritonavir, gastrointestinal side effects should be monitored for and timely intervention provided. Thirdly, for feeding, the enteral route should be the first choice. In patients undergoing mechanical ventilation, establishing a jejunal route as early as possible can guarantee the feeding target being achieved if gastric dilatation occurs. Fourthly, we suggest a permissive underfeeding strategy for severe/critical patients admitted to the intensive care unit during the first week of admission, with the energy target no more than 20 kcal/kg/day (for those on mechanical ventilation, this target may be lowered to 10–15 kcal/kg/day) and the protein target around 1.0–1.2 g/kg/day. If the inflammatory condition is significantly alleviated, the energy target may be gradually increased to 25–30 kcal/kg/day and the protein target to 1.2–1.5 g/kg/day. Fifthly, supplemental parenteral nutrition should be used with caution. Lastly, omega-3 fatty acids may be used as immunoregulators, intravenous administration of omega-3 fatty emulsion (10 g/day) at an early stage may help to reduce the inflammatory reaction.

Key words: COVID-19, Intensive care, Nutritional risk, Nutritional support, Energy, Protein, Omega-3 fatty acids, China, Gut, Metabolism

Highlights

- Although the COVID-19 pandemic is a global crisis, research that focuses on the relationship between gut, metabolism and nutritional support in this disease is still scarce.
- The persistent hypoxia and consequent compensatory processes in the COVID-19 patient make the gastrointestinal system, after the lungs, an early target. In addition, the gut side effects of widely used antiviral regimens can aggravate the gut injury and significantly increase nutritional risks.
- We recommend using the Nutritional Risk Screening 2002 screening tool to assess all hospitalized COVID-19 patients, with immediate commencement of oral nutritional supplements in those whose score is ≥ 3.
- We suggest a permissive underfeeding strategy (20 kcal/kg/day energy intake, 1.0–1.2 g/kg/day protein intake) for severe patients during the first week of admission to the intensive care unit, with gradual increases of these targets as symptoms rescind.
- The enteral route should be the first choice. For patients being ventilated,, if the gastric dilatation occurs, we recommend establishing a jejunal route as early as possible to ensure that the feeding target can be achieved.

Background

The COVID-19 pandemic has been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as named by the International Committee on Taxonomy of Viruses. Up to the end of November 2020, the number of worldwide confirmed cases has dramatically increased to nearly 60 million, causing nearly 1.4 million deaths [1].

The typical symptoms for most patients are respiratory, such as coughing and difficulty breathing. However, physicians and researchers soon discovered that gastrointestinal symptoms may also be initial signs for many patients [2]. Molecular studies have shown that the organs affected by SARS-CoV-2 are not only those of the respiratory system: the gastrointestinal system is also targeted by the virus [3]. These findings indicate that the gastrointestinal system plays an important role in the development of this disease and that metabolic and nutritional support in the treatment of COVID-19 warrants our attention. However, to date, we have found very little research that focuses on the relationships between the gut, metabolism, nutritional support and COVID-19, and few direct clinical studies have been published on nutritional intervention in COVID-19 patients.

Since March 2020, the National Commission of Health of China [4], the European Society for Parenteral and Enteral Nutrition (ESPEN) [5] and the American Society for Parenteral and Enteral Nutrition (ASPEN) have successively launched their expert consensus or guidance documents on nutritional support for COVID-19 patients [6]. These guidelines provide systematic and comprehensive principles. However, the relationship between SARS-CoV-2 and gastrointestinal injuries have not received sufficient attention in the global COVID-19 research community. In addition, the recommended nutritional support targets from these guidelines are inconsistent (Table 1) [4, 5, 6], and this situation may confuse practitioners on the frontline.

Almost everywhere around the world, a lack of medical resources and medical personnel is common, as almost everyone is overworked. Considering this situation, the purpose of this review is to provide simple, actionable suggestions. We hope this work will be of use to our colleagues fighting this disease worldwide by providing them with a concise picture of the roles of metabolic and nutritional support, which may assist them in developing personalized treatment strategies.

Review

The gastrointestinal system is one of the most affected target organs after the lung

This pandemic emerged as respiratory transmitted disease, thus scientists and physicians paid most attention to the relationship between the lung and the virus. Studies have demonstrated that SARS-CoV-2 enters alveolar type 2 cells through the angiotensin-converting enzyme 2 receptor and causes subsequent injuries to the lung. Most patients recover under appropriate treatment and support. However, the conditions of some patients may suddenly deteriorate and quickly progress to multi-organ dysfunction, and even death. The reasons that this deterioration occurs are still yet to be completely understood. Some research indicates that, under continuous attack from the virus, large amounts of pro-inflammatory cytokines are released (cytokine storming), resulting in catastrophic injuries to many organs and systems [7, 8].

In fact, molecular pathology studies have revealed that the targets of SARS-CoV-2 are not limited to the respiratory system—the heart, esophagus, intestines and kidneys are also affected [3]. Anatomical and autopsy studies on deceased patients have shown that the intestinal epithelium shrinks, gut barriers are destroyed and there are signs of enteroparalysis [9, 10]. These findings suggest that the gastrointestinal system, like the respiratory system, is also attacked by SARS-CoV-2.

The persistent hypoxia and consequent compensatory processes play a key role in the evolution of a patient's condition from mild to severe [11]. The redistribution of circulation and the ensuing ischemia–reperfusion will occur in the very early stages for severe patients. The gastrointestinal system has been demonstrated to be the earliest victim in this process,

Table 1. Feeding targets recommended by international nutritional medicine societies for patients with COVID-19

Guidelines	Energy target	Protein target
National Health Commission of China	25–30 kcal/kg/day	1.5–2.0 g/kg/day
American Society for Parenteral and Enteral Nutrition	15–20 kcal/kg/day	1.2–2.0 g/kg/day
European Society for Parenteral and Enteral Nutrition	27 kcal/kg/day (polymorbid patients aged >65 years) 30 kcal/kg/day (severely underweight polymorbid medical inpatients patients; older persons)	1 g/kg/day (older persons) ≥1 g/kg/day (polymorbid medical inpatients)

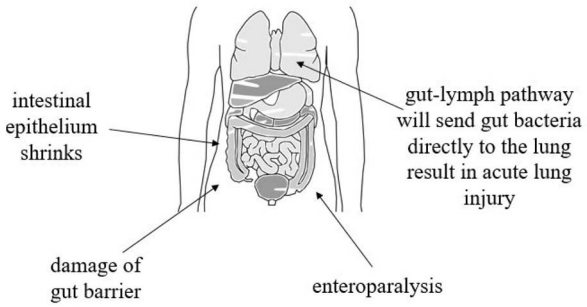

Figure 1. Pathophysiological mechanisms of COVID-19 in the gut

as the gut is deprived of blood supply. Hypoxia of the gut occurs soon after the lungs are affected, before any other organ. Over the past 40 years, numerous researchers, including the authors, have demonstrated that there are at least two ways that gut bacteria may transfer to the circulation and injure organs remotely: (1) damage of the gut barrier causes bacteria to transfer to the blood and cause sepsis; and (2) the gut–lymph pathway sends gut bacteria directly to the lungs, resulting in acute lung injury [12–15]. This is what we term "gut-centered injury" in COVID-19 patients. We pointed out specific COVID-19-related targets in Figure 1 and summarized the research actualities on target organs of SARS-CoV-2 in Table 2.

At present, no widely approved vaccine exists for COVID-19. In contrast to other viral infections, we only have limited antiviral regimens, such as lopinavir/ritonavir (LPV/r) [4, 26, 27]. LPV/r is a widely used anti-HIV drug and patients frequently report gut-related side effects. The occurrence of anorexia, nausea, vomiting and diarrhea is around 20% among the population of patients with HIV [28]. However, we have found that, in COVID-19 patients who receive treatment with LPV/r, the frequency of gut side effects is significantly higher than the patients who did not receive LPV/r. In clinical practice, we have observed the rate of gut side effects to be around 50%, and Pan *et al*. have reported similar findings, namely that patients who received LPV/r reported a significantly higher rate of gastrointestinal symptoms [2]. It is reasonable to extrapolate that this is the combined result of the side effects of LPV/r and the attack of the virus on the gut. In addition, psychosomatic factors are extremely important in the development of the disease from mild/moderate to severe/critical. Because of the high infection rate, high death risk and the significant amount of negative information from the media, patients are under persistent anxiety and physiological stress. Furthermore, during quarantine, narrow spaces and tasteless hospital food do not help the mood of patients. Anorexia impedes energy and protein intake, quickly causing malnutrition and worsening the immune system. This vicious combination can aggravate mild-to-moderate cases, causing them to become severe.

Nutritional screening and evaluation Based on the above analysis, COVID-19 patients are at very high risk for malnutrition. Evaluation of a patient's nutritional risks should be routine at admission, and this requires selection of an appropriate nutritional risk evaluation tool: for this, we suggest the Nutritional Risk Screening 2002 (NRS-2002) system. The NRS-2002 is an easy-to-use, efficient and highly sensitive tool that is accepted by health practitioners worldwide [29]. In general, patients with an NRS-2002 score <3 are treated as having no nutritional risk, indicating that nutritional support is not required during the first week of hospitalization. However, the authors wish to stress that most COVID-19 patients are of good nutritional status at admission, with the first NRS-2002 screening score usually <3. However, as the disease progresses and of antiviral regimens are commenced, gastrointestinal symptoms will appear. Food intake reduction, nausea, diarrhea and being confined to bed will cause a rapid loss of lean body mass loss; therefore, admission screening, with re-screening the following week, cannot be relied upon. According to our observations, the NRS-2002 scores of patients tend to increase 3–5 days after admission. We therefore recommend that all hospitalized COVID-19 patients be periodically screened using the NRS-2002 (Once every 3–5 days). When the score is ≥3, nutritional intervention should be commence immediately. Considering the shortage of dietitians and nurses, we suggest that these patients receive oral nutritional supplements initially, using any enteral nutrition product or food for special medical purposes that patients will accept [30].

NRS-2002 versus Nutrition Risk in Critically Ill (NUTRIC) score for severe patients

Some experts suggest that, for severe COVID-19 patients, the NUTRIC score is a better tool than the NRS-2002 from

Table 2. Published researches on target organs of SARS-CoV-2 and pathophysiological mechanisms

Authors	Country	Year (month)	Type	Target organs and major mechanisms
Yao *et al.* [16]	China	2020 (March)	Pathological report	SARS-CoV-2 is mainly distributed in lungs; it also affects the immune system, cardiovascular system, liver and kidneys. The mechanism needs further study.
Yang *et al.* [17]	China	2020 (February)	Review	In addition to the respiratory system, the kidney is also one of the target organs. There are three possible mechanisms: (1) SARS-CoV-2 attacks the kidney directly through ACE2 receptor; (2) immune-mediated injury; (3) sepsis/septic shock.
Fang *et al.* [18]	China	2020 (February)	Single-center descriptive study	Most COVID-19 patients have significant manifestation of gastrointestinal system issues, including diarrhea, nausea and stomachache. The main mechanism may be high expression of ACE2 in the gastrointestinal system.
Zhang *et al.* [19]	China	2020 (February)	Observational study	SARS-CoV-2 was detected in an anal swab and blood. Its mechanism is not completely clear. Infected patients can potentially spread SARS-CoV-2 through respiratory, fecal–oral or body-fluid routes.
Pan *et al.* [20]	China	2020 (March)	Descriptive multicenter study	Digestive symptoms are common in COVID-19 patients and last a long time. There are many possible mechanisms: (1) SARS-CoV-2 attacks the gastrointestinal system directly through ACE2 receptor; (2) immune-mediated injury; (3) SARS-CoV-2 may cause disorders of the intestinal flora.
Song *et al.* [21]	China	2020 (March)	Case reports	Diarrhea was the onset symptom in a patient with COVID-19. Its mechanism is not completely clear, but the gastrointestinal system may be a potential route of SARS-CoV-2 invasion and transmission.
Bourgonje *et al.* [22]	The Netherlands	2020 (July)	Review	ACE2 expression and activity may lead to ARDS and multiorgan failure. ACE2 was highly expressed on lung alveolar epithelial cells and small intestinal epithelial cells.
Smyk *et al.* [23]	Poland	2020 (September)	Review	Gastrointestinal symptoms (diarrhea, vomiting, nausea or abdominal pain) were frequent in patients with COVID-19, due to the abundant expression of ACE2 in the gastrointestinal tract.
Bradley *et al.* [24]	USA	2020 (July)	Case series	Coronavirus-like particles were detected in the respiratory system, kidney and gastrointestinal tract.
Mitsuyama *et al.* [25]	Japan	2020 (November)	Review	Along with the respiratory tract, the gastrointestinal tract is one of the main extra-pulmonary targets of SARS-CoV-2 with respect to symptom occurrence and is a potential route for virus transmission, most likely due to the presence of ACE2.

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, *ACE2* angiotensin-converting enzyme 2, *ARDS* acute respiratory distress syndrome

a practical viewpoint, the authors do not agree with this. At the epicenters of the pandemic, almost all intensive care units (ICUs) are full, with both the workflow and workload completely different to normal. In short, the number of patients in the ICU has surged and the physicians and nurses are overwhelmed. The Sequential Organ Failure Assessment score is the most important component of the NUTRIC score, but its calculation relies on the results of many laboratory tests—in such chaotic circumstances, we cannot expect these tests to be readily available for every patient who is sent to the ICU. We also cannot expect the physicians and nurses to have enough time and attention to use the NUTRIC for nutritional assessment. In addition, even under normal situations, NUTRIC is not regularly used in every ICU case and staff may not be familiar with it, making its use impractical [31].

Metabolic disturbances and feeding targets in severe patients

To determine a patient's feeding target is not an easy task, especially in severe patients. One should carefully consider the

complicated relationships between metabolic disturbances, nutritional requirements and the tolerance of organs to the nutritional substrates provided. We must remember that these relationships are constantly changing and evolving in different phases during the progression of severe/critical patient's condition. Both overfeeding and underfeeding risk unbalancing metabolism and can lead to death. According to the recommendations of major international clinical nutrition academic organizations (e.g. ESPEN and ASPEN), the best way to determine a patient's energy needs is to measure the resting energy expenditure (REE) using indirect calorimetry [32, 33]. In our experience, however, this is not feasible in an ICU overcrowded with patients. Singer *et al.* and Zusman *et al.* provided us with an alternative solution [34, 35]. In their studies, they found the ratio of administered calories to REE is significantly associated with mortality. When the ratio is 0.7–0.8, risk of death is at the lowest level. The average REE in their study was around 25 kcal/kg, 70–80% of 25 kcal/kg is 18–20 kcal/kg; this is exactly the strategy that "permissive underfeeding" promotes. Over the past decades, many researchers, including the authors, have demonstrated that a short period of permissive underfeeding is beneficial for severely ill patients and those undergoing surgeries [36], a recent study by McKeever *et al*. provides further evidence that lower calorie intake during the first week of hospitalization will reduce the level of oxidative stress for ventilated patients on mechanical ventilation [37]. Based on this evidence, and considering the severe oxidative stress status of COVID-19 patients, we recommend an early permissive underfeeding strategy on energy provision in the first week of ICU stay, with a target of 20 kcal/kg/day. For mechanically ventilated patients, the target should be reduced to 10–15 kcal/kg/day. As inflammatory processes recede, the energy provision may be increased gradually, eventually reaching 25–30 kcal/kg/day, in order to avoid the energy debt that results from long-term underfeeding.

Protein: less or more?

In the current Chinese guidelines, an increased provision of protein, 1.5–2 g/kg/day, is recommended [38]; ASPEN guidelines recommend 1.2–2.0 g/kg/day [6]. However, this is challenged by the results of clinical trials. Findings from randomized controlled trials indicate that provision of 1.5 g/kg/day protein does not significantly improve the outcomes compared with 1.0 g/kg/day [39, 40, 41]. Given the inflammatory processes seen in severely ill patients, high levels of protein intake may aggravate the situation. In addition, no current enteral nutrition product can meet the 1.5–2.0 g/kg/day target. In fact, to reach this, nurses would be required to add protein powder into enteral nutrition (EN) products, and this would add additional risks: first, it is impossible to provide the many specific sterile preparation rooms that would be required for this procedure; and second, nutritional nurses are already overworked and do not have time to train junior nurses. The result would be that contaminated protein products would be administered to patients. Therefore, we recommend a moderate protein provision, around 1.0–1.2 g/kg/day, which is similar to that recommended in the ESPEN guidelines [5].

Feeding approach

The enteral route should be the first choice. We have observed that gastric dilatation is very common in severe/critical patients receiving mechanical ventilation therapy, especially those who are mechanically ventilated in the prone position. Tube feeding through gastric route is hard to reach feeding target and may cause EN failure. We recommend establishing the jejunal route as early as possible. Continuous pump-based jejunal feeding is preferred, and it may reduce the risk of aspiration. Given the extreme shortage of physicians and nurses, as well as medical devices, it is almost impossible to reach the 25–30 kcal/kg/day feeding target via the enteral route during the early stage of treatment in critical illness patients. If the guidelines insist, supplemental parenteral nutrition (SPN) is inevitable. This leads to another long-term controversy in giving SPN to these patients: whether SPN can improve critical illness patients' outcomes? [39] Since 2011, many large-scale clinical trials have found that early SPN does not confer benefit in patients admitted to the ICU [42–44]. For critical COVID-19 patients, one major pathophysiological development is the retention of water and sodium, lung edema and subsequent hyaline membrane formation. Limiting intravenous fluid is an important strategy in this situation. SPN is the easiest way to provide energy and amino acids, but it increases the risk of fluid overloading. Overall, we suggest cautious usage of SPN to avoid fluid overload and bloodstream infection.

Pharmaceutic nutrients

Over the last three decades, several nutrients that confer benefit beyond simply providing energy or nitrogen have been identified: omega-3 fatty acids (omega-3 FAs), glutamine, arginine and branched-chain amino acids, among others. Researchers have concluded that arginine cannot be used on severe patients with high inflammation status. Both omega-3 FAs and glutamine have complex metabolic and immunomodulatory mechanisms, which have become the focus of research and debate.

Omega-3 FAs Some guidelines recommend omega-3 FAs enhanced products for severe/critical patients. For example, Chinese Guidelines for Severe COVID-19 recommends omega-3 enhanced enteral nutrition. It also recommends adding fish oil emulsion into parenteral nutrition. In section 4, article 7; the specific statement is "severe COVID-19 patients may be administered EN products enhanced by Omega-3 fatty acids. Their PN may add fat emulsion enhanced by EPA and DHA". From our perspective, the central issues around using omega-3 fatty acids in patients with severe COVID-19 are formulations, dosage and timing. The formulations

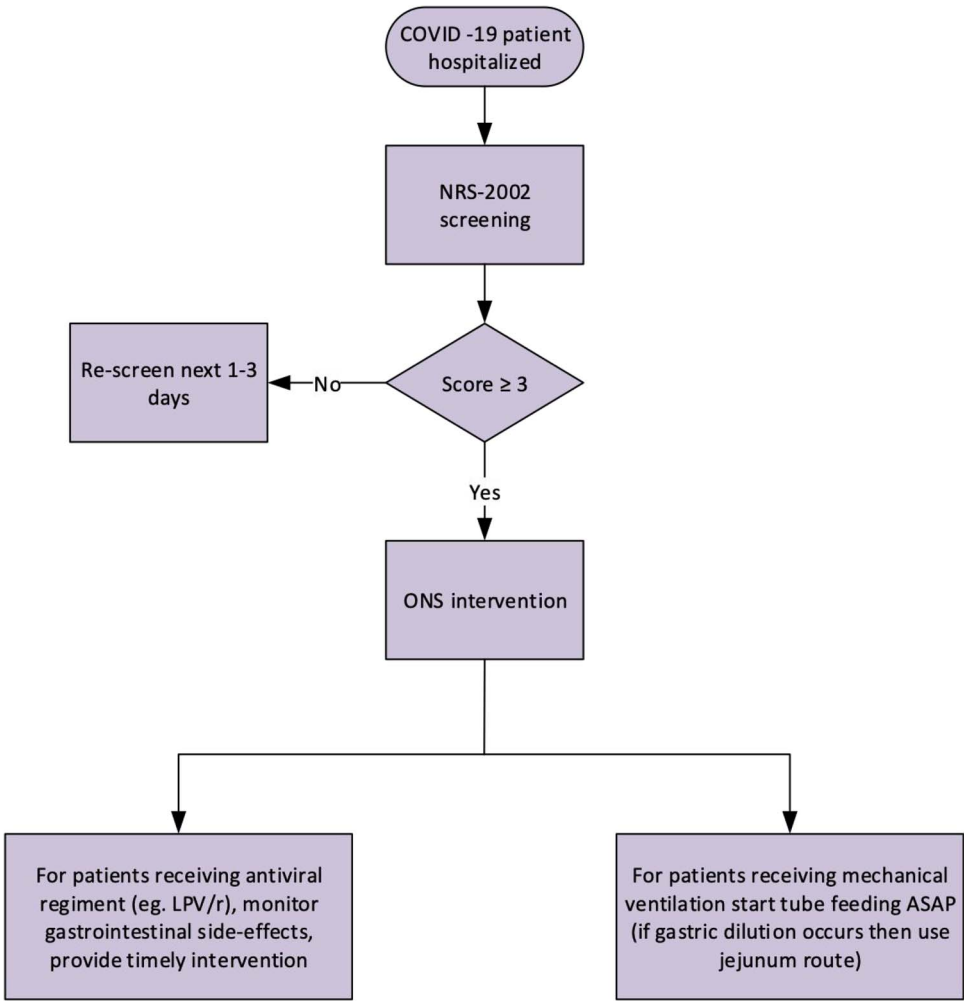

Figure 2. Algorithm for nutritional management in COVID-19 patients. *NRS-2002* Nutritional Risk Screening 2002, *ONS* oral nutritional supplements, *LPV/r* lopinavir/ritonavir

of omega-3 FAs include a parenteral formulation and so-called "immune enhanced EN products" that contain omega-3 FAs. Thus, there are three forms in which omega-3 FAs may be administered: (1) sole infusion omega-3 FAs emulsion is used for down-regulating pro-inflammatory status; (2) adding omega-3 FAs to parenteral nutrition (PN) to elevate the ratio of omega-3/omega-6 [45]; and (3) using immune-enhanced EN products that contain omega-3 FAs. If one aims to downregulate the inflammatory reaction, the sole infusion of omega-3 FAs has its rationale, especially for severe patients at early phase. It may inhibit the formation of cytokine storm that is still during fermentation. Second, if the enteral route is not available and PN is indicated, adding omega-3 fatty acids into the PN is an alternative. However, it is not inconclusive that omega-3 FAs enhanced EN products can inhibit cytokines storm and make positive outcomes. From 2016 to 2019, there was no international consensus reached on this issue (including guidelines from ASPEN, ESPEN and other academic organizations) and the debate continues [46, 47]. In fact, every immune-enhanced EN product is a complex compound that contains at least one or more functional components in addition to omega-3 FAs (e.g. vitamin D, arginine, nucleosides and others). Which, if any, components are detrimental and which are beneficial, especially on a background of metabolic disturbance, remains unclear. From a clinical perspective, the major problem of severe critical COVID-19 patients is severe hypoxia and acute lung injury [48]. Given the current evidence, we would suggest very careful use of immune-enhanced EN products containing omega-3 FAs.

Glutamine Glutamine is an essential amino acid that is often administered when enteral nutrition is not available [49]. However, as the study conducted by Heyland DK et al. has shown, in patients with kidney problems, it may be a toxin [50]. Considering the kidney is a target organ of SARS-CoV-2, and acute kidney injury is a major risk for severe COVID-19 patients, we would not suggest the use of glutamine.

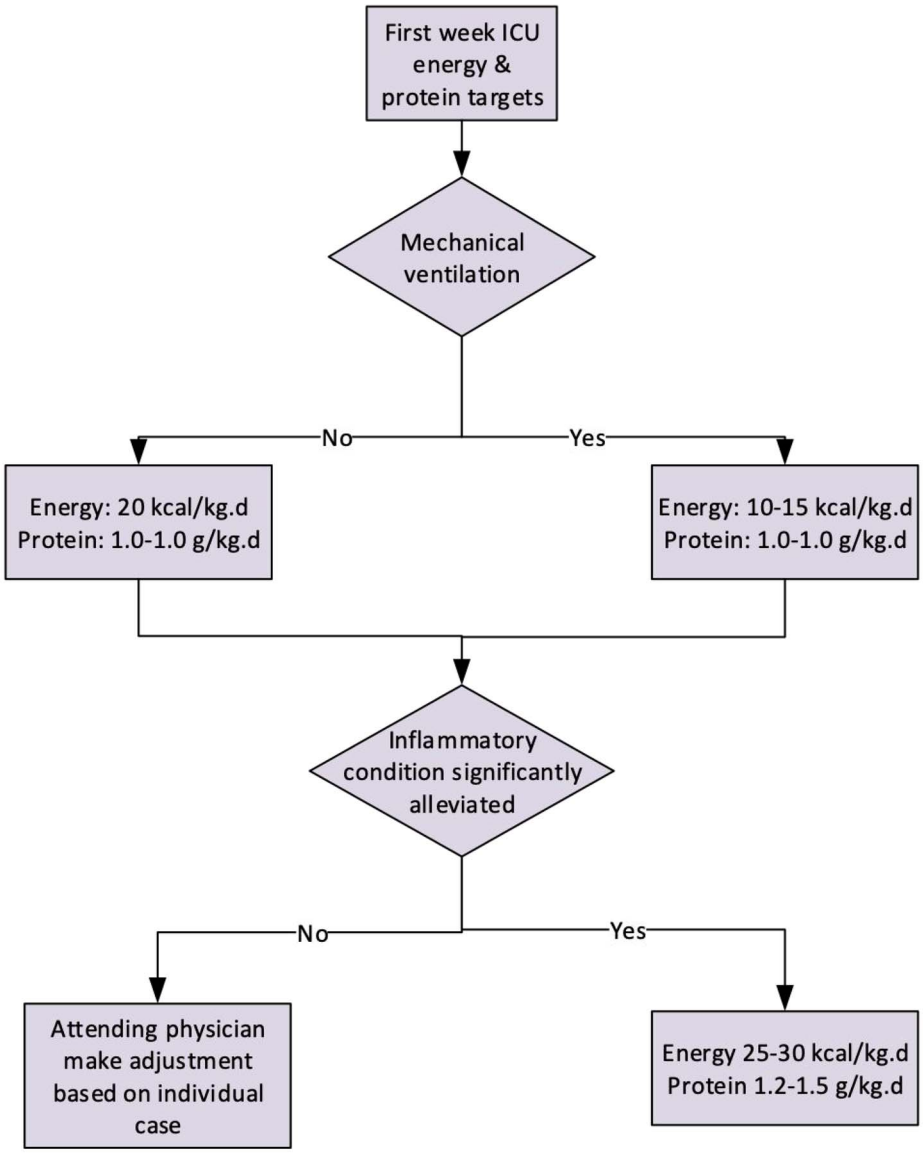

Figure 3. Energy and protein intake targets for severe patients. *ICU* intensive care unit

Table 3. Major recommendations regarding nutrition management for COVID-19

Major recommendations	
Nutritional risk evaluation	(1) Use of the Nutritional Risk Screening 2002 system should be routine and the first-choice screening tool. If the score is ≥3 at first screening, oral nutritional supplements should be given immediately; otherwise, secondary screening should be conducted in the following 1–3 days. (2) Possible acute gut injury should be closely monitored for.
Side effects of antiviral treatment	(1) Attention should be paid to side effects of antiviral treatment and timely intervention provided.
Nutrition route	(1) The enteral route should be the first choice. (2) Supplemental parenteral nutrition should be used with caution.
Site and infusion of EN	(1) The jejunal route should be established as early as possible, due to the risk of gastric dilatation. (2) Pump-based jejunal feeding should be used to reduce the risk of aspiration.
Energy and protein targets	(1) A permissive underfeeding strategy is of optimum benefit during the first week of ICU admission. The energy target should be no more than 20 kcal/kg/day (target may decrease to 10–15 kcal/kg/day during mechanical ventilation). (2) After the inflammatory phase, the energy target may be gradually increased to 25–30 kcal/kg/day and the protein target to 1.2–1.5 g/kg/day.
Pharmaceutical nutrients	(1) Intravenous omega-3 fatty acid emulsion (10 g/day) should be used at an early stage. (2) The routine use of glutamine is not currently recommended.

Overall, the suggestions for the metabolic and nutritional management of COVID-19 patients are summarized in Table 3, and the operational procedures are detailed in Figures 2 and 3.

Conclusions

For any patient who is diagnosed with COVID-19, we suggest the following metabolic and nutritional management. (1) NRS-2002 screening shall be conducted routinely and periodically. For patients whose score ≥ 3, ONS should be given immediately. For patients whose score <3 at the time of first screening, secondary screening should be conducted in the following 1–3 days, with systematic evaluation for possible acute gut injury. The goal here is to prevent malnutrition that could lead to progression to a more severe illness status or death. (2) For patients receiving antiviral regimens, such as LPV/r, attention should be paid to gastrointestinal side effects and timely intervention provided. (3) Gastric dilatation is common in severe/critical patients receiving mechanical ventilation therapy. Tube feeding via the gastric route is hard to reach feeding target and may cause EN failure. We recommend establishing the jejunal route as early as possible. Continuous pump-based jejunal feeding is recommended, and it may reduce the risk of aspiration. (4) For energy and protein targets, we suggest a permissive underfeeding strategy during the first week of ICU admission, with an energy target of no more than 20 kcal/kg/day (for patients on mechanical ventilation, this may be decreased to 10–15 kcal/kg/day) and a protein target of around 1.0–1.2 g/kg/day. If the inflammatory condition is significantly alleviated, the energy target may be gradually increased to 25–30 kcal/kg/day and the protein target increased to 1.2–1.5 g/kg/day. (5) The enteral route should used as early as possible; SPN should be used with caution. (6) For pharmaceutic nutrients, omega-3 FAs may be used as an immunoregulatory drug. We suggest the use of intravenous omega-3 FA emulsion at an early stage in a dosage of 10 g/d. The use of glutamine is not recommended routinely.

Abbreviations

ASPEN: American Society for Parenteral and Enteral Nutrition; ESPEN: European Society for Parenteral and Enteral Nutrition; ICU: intensive care unit; LPV/r: lopinavir/ritonavir; NRS-2002: Nutritional Risk Screening 2002; NUTRIC: Nutrition Risk in Critically ill; omega-3 FAs: omega-3 fatty acids; EN: enteral nutrition; PN: parenteral nutrition; REE: resting energy expenditure; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SPN: supplemental parenteral nutrition

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Authors' contributions

HJ and WC conceptualized the review and lead the writing. JCZ, JZ, LW, YW, HFD and KW completed literature retrieval and information extraction. HJ and CDL drafted the manuscript. CDL contributed to visualization. HJ, WC, JZ, MWS, LD and PZ provided their clinical experiences. HJ, WC and CDL reviewed and edited the final version of the manuscript. All authors approved the manuscript.

Conflicts of interest

All authors declare that they have no competing interests.

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