

# Clinical nutrition approach in medical management of COVID-19 hospitalized patients: A narrative review

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## Abstract

**Background:** Malnutrition in COVID-19 hospitalized patients is associated with a high-risk condition to increase disease severity and prolonging the recovery period. Therefore, nutritional therapy, including supplements plays a critical role to reduce disease-related complications and the length of hospital stay.

**Aim:** To review the latest evidence on nutritional management options in COVID-19 hospitalized patients, as well as possibly prescribed supplements. **Methods:** This review was conducted by considering the latest recommendations, using the guidelines of the American Society of Enteral and Parenteral (ASPEN) and the European Society of Enteral and Parenteral (ESPEN), and searching Web of Science, PubMed/Medline, ISI, and Medline databases. The relevant articles were found using a mix of related mesh terms and keywords. We attempted to cover all elements of COVID-19 hospitalized patients' dietary management. **Results:** Energy demand in COVID-19 patients is a vital issue. Indirect Calorimetry (IC) is the recommended method to measure resting energy expenditure. However, in the absence of IC, predictive equations may be used. The ratio of administered diet for the macronutrients could be based on the phase and severity of Covid-19 disease. Moreover, there are recommendations for taking micronutrient supplements with known effects on improving the immune system or reducing inflammation. **Conclusions:** Nutritional treatment of COVID-19 patients in hospitals seems to be an important element of their medical care. Enteral nutrition would be the recommended feeding method for early nutrition support. However, data in the COVID-19 nutritional domain relating to micronutrient supplementation are still fragmentary and disputed, and further study is required.

## Keywords

Clinical nutrition management, COVID-19, hospitalized patients, micronutrient supplements, review

## Background

The outbreak of coronavirus (known as COVID-19), which was initially reported in December 2019 in Wuhan, China, is widely spread worldwide which is reported as a pandemic by World Health Organization on March 11, 2020 (World Health Organization, 2020a). The COVID-19 asymptomatic infected subjects would be major virus carriers, and symptomatic patients present clinical characteristics such as respiratory and gastrointestinal disorders in various ranges of disease severity (World Health Organization, 2020b). Patients with severe symptoms of the virus, particularly those involving the respiratory system, may need to be admitted to the hospital and perhaps to the Intensive Care Unit (ICU) (World Health Organization, 2020b). Because it is a new virus with an unknown attitude, therapy is difficult (Cortegiani et al., 2020).

COVID-19, like other infectious diseases, is considered a high-risk state for nutrition deterioration (Jin et al., 2020). Malnourished patients are more susceptible to be

symptomatic following the virus infection, and they have a higher rate of hospitalization requirement (in terms of severe acute respiratory infection (SARI)), deteriorated clinical outcomes, and disease-related complications (Huang et al., 2020; Katona and Katona-Apte, 2008).

Fever, cough, myalgia, fatigue, dyspnea, and even gastrointestinal symptoms such as diarrhea, nausea, and

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vomiting are common in SARS-Cov-2 patients (Huang et al., 2020), all of which might have a major impact on nutrition intake. Anorexia and poor nutrition intake are also caused by high plasma levels of inflammatory cytokines (Huang et al., 2020). The increase of resting energy expenditure in the field of infection, inflammation, and fever and the decrease of nutrition intake can lead to protein-energy malnutrition in these patients, and malnutrition may worsen the condition by weight loss, mucosal damage, and lowered immunity in a defective cycle (Katona and Katona-Apte, 2008). The patients with severe pneumonia are at risk for malnutrition because of decreased intake and the severity of symptoms.

According to available data, 26.1% of hospitalized patients with COVID-19 are admitted to the ICU because of different complications. Most of patients are in the inflammatory state which can lead to increased resting energy expenditure (Pratt et al., 1979). The ventilation can alter the nutrition intake, so the patients are more at risk for malnutrition. Decreased energy and nutrient intake which is particularly prevalent in severely ill COVID-19 patients and during the acute phase of stress, as well as the potentially increased energy expenditure following disease severity and complications may lead to malnutrition development and subsequently worsen the prognosis and clinical outcomes (Huang et al., 2020; Katona and Katona-Apte, 2008). Underfeeding increases the risk of infection, breathing muscle atrophy and decreased muscular strength, immunosuppression, and inability to wean off mechanical ventilation in critically ill patients. Hence, malnutrition can cause increased morbidity, mortality, length of stay, and ventilation (Krzak et al., 2011).

On the other hand, overfeeding such patients may deteriorate the patient's clinical condition and prolong the ventilation period (De Waele et al., 2021). It is aligned with electrolyte imbalance, hyperglycemia, azotemia, hypercapnia, and prolonged ventilation.

Recent data showed that the state of nutrition at the time of admission in COVID-19 old patients is associated with length of stay (Mendes et al., 2021) which can be emphasized the importance of nutrition in this disease, especially from the first days of diagnosis. Therefore, medical nutrition therapy (MNT) of patients with the diagnosis of COVID-19 as a therapeutic approach in parallel to other aspects of their medical management would be of great importance (Aman and Masood, 2020; Khayatzadeh, 2020; Medeiros de Morais, 2021). Thus, MNT should be considered for them. Food intake in some patients seriously decreases and sip feeding and even enteral feeding are needed. MNT should be considered and recommendations for the patients with mild illness and continue in severe pneumonia.

The purpose of this narrative review was to offer updates on nutritional management options in COVID-19 hospitalized patients, including nutritional evaluation, intervention, and monitoring, as well as possibly prescribed supplements.

## Literature search

In the current narrative review, two main sources were used for data gathering:

First, to collect the new advice on *macronutrients*, the latest guidelines of the American Society of Enteral and Parenteral (ASPEN) and the European Society of Enteral and Parenteral (ESPEN) were critically reviewed. Second, the authors focused on published articles to find out new data on *micronutrient* therapy in COVID-19 treatment. To this end, two electronic databases (PubMed/Medline, ISI Web of Knowledge) were searched in April 2021 for the English language published articles (both original and review articles) to investigate the following topics: articles on micronutrient therapies in *viral pneumonia*, articles focused on micronutrient therapies in Severe Acute Respiratory Syndrome (*SARS*) and Middle East respiratory syndrome (*MERS*); finally, the randomized controlled trials recently published in the administrations of micronutrients among COVID-19 patients. We have searched via the references of the related article and used the full-texts.

## Results

### *Medical nutrition therapy in COVID-19*

A stepwise algorithmic nutrition support program may improve nutritional adequacy indices in COVID-19 patients. An initial nutritional assessment followed by a customized interventional protocol with a documented monitoring process is necessary for all hospitalized patients. Validated screening tools may help detect patients' requirements for specialized assessment. Nutrition support for hospitalized patients should be started as soon as possible following the hemodynamic stability of the patients.

### *Time to start nutrition support*

According to recent evidences enteral (EN) nutrition shall be started 24–48 h after admission in the ICU to decrease complications (Lambell et al., 2020). EN shall be preferred to parenteral nutrition (PN) when EN is not contraindicated (Singer et al., 2019), and early EN shall be considered rather than delayed EN (Singer et al., 2019) in all well-nourished, moderately malnourished and severely malnourished patients in the acute early phase (ICU day 1–2) (Lambell et al., 2020). In hypotensive patients or the state of increasing doses of vasopressors, EN shall be withhold (Singer et al., 2019).

### *Route for nutrition support*

Oral nutrition support, comprising dietary advice for a well-balanced diet, including optimal calorie and protein intake, as well as enough fruit and vegetable consumption, is required for patients in the moderate state of COVID-19. Sip feeds are necessary for patients with inadequate intake. EN

shall be preferred to PN when EN is not contraindicated (Singer et al., 2019) and early EN shall be considered rather than delayed EN (Singer et al., 2019) in all well-nourished, moderately malnourished, and severely malnourished patients in acute early phase (ICU day 1–2) (Lambell et al., 2020). After the patients become extubated, the consistency of the food should be changed (puree or soft food), and if there is a swallowing disorder, intestinal feeding should be performed. To rule out the existence of a very high risk of aspiration, post-pyloric nutrition and if this is not possible, temporary parenteral nutrition is recommended at the same time as swallowing therapy.

**Energy supply and nutrition support macronutrients' ratio.** In Covid-19 patients, optimal energy administration is regarded a critical component of effective. In practice, estimating energy consumption using predictive equations is a regular problem. Previous formulae, on the other hand, were unable to effectively estimate resting energy metabolism in various stages and severity levels of the illness. Therefore, it would strongly recommend assessing energy requirements by indirect calorimetry (IC) as the standard method.

Although IC is recommended for energy estimation by ASPEN and ESPEN guidelines (McClave et al., 2016; Singer et al., 2019), ESPEN guideline indicated that using VCO<sub>2</sub> (carbon dioxide production) derived from the ventilator in the formula of “REE  $\frac{1}{4}$  VCO<sub>2</sub> 8.19” or VO<sub>2</sub> (oxygen consumption) from the pulmonary arterial catheter is preferred for evaluating energy expenditure than predictive equations, such as 20–25 kcal/kg/d. The authors of the aforementioned guideline included “the simplest option may be preferred” (Singer et al., 2019). However, for obese patients (body mass index >30 Kg/m<sup>2</sup>) adjusted body weight instead of actual weight is used in predictive equations (Lambell et al., 2020). Therefore practical recommendations for COVID-19 patients (Table 1) would be as follows:

**Calorie intake in the acute early phase.** Well-nourished and moderate malnutrition patients: most parts of the estimated calorie (70%) should be supplied from EN route. (Singer et al., 2019) Severely malnourished patients: Estimated energy requirement should be gradually considered to almost 50% of target energy in the early acute phase, and signs for refeeding syndrome (especially hypophosphatemia) should be monitored (Lambell et al., 2020).

**Calorie intake in the acute late phase (ICU day 3–7).** Well-nourished and moderate malnutrition patients: EN will continue. PN should be considered in case of EN contraindications or if calorie supplementation is not adequate (<60% of estimated calorie) (Lambell et al., 2020; McClave et al., 2016; Singer et al., 2019). In obese patients with a BMI range of 30–50, energy requirement should be estimated as 11–14 Kcal/Kg (of Ideal body weight) and 22–25 Kcal/Kg for BMI >50 (McClave et al., 2016). Patients

with severely malnourished: EN will continue, in case of EN contraindications or if calorie supplementation is not adequate (60%), PN should start and gradually progress, along with observations for refeeding signs (Lambell et al., 2020).

**Calorie intake in the recovery phase (ICU >7 days).** Nutrition support for an energy target of 80–100% of estimated energy should be continued (Lambell et al., 2020).

The macronutrients' ratio of administered diet for such patients would be based on the past medical history as well as the clinical manifestation, phase, and severity of Covid-19 disease.

**Micronutrient supplementation.** Micronutrients have a significant role in the prevention, treatment, and improvement of viral respiratory infections as part of medical nutrition therapy (Rice 2012). By reducing food intake, increasing loss, and increasing daily needs, a critical disease condition may lead to micronutrient shortages and, as a result, immune function disorders (Reintam Blaser et al., 2016). In a situation, deficiencies, especially zinc, selenium, thiamine, folate, vitamin B12, vitamin D, and vitamin C may be seriously presented (Casaer and Bellomo, 2019).

Adequate amounts of all micronutrients are essential for the efficient function of immune system (Maggini et al., 2018). So, RDA doses of all micronutrients should be provided for all COVID-19 patients. Furthermore, they should be screened for potential deficiencies and subsequently require supplementations. There is a list of minerals and vitamins that maintain immune function. Vitamins A, B6, B12, C, D, E, folate, zinc, and Iron have a major role in maintaining the functional and structural integrity of mucosal cells (Reintam Blaser et al., 2016). The role of zinc, iron, copper, selenium, magnesium, and vitamins A, D, E, C, and B6 in inflammation is described as well (McMillan et al., 2019). Recent research has shown a link between respiratory infections and the deficiency in some micronutrients. Vitamin C and D deficiency are linked to an increased risk of pneumonia and its severity (Wang et al., 2019a). In the case of respiratory infections, vitamin D deficiency has an impact on mortality and morbidity (Charoenngam et al., 2021). Zinc deficiency which is more common in children and elders, increases the risk of viral infections and morbidity (Gombart et al., 2020). Moreover, elders and patients with underlying diseases are most susceptible to micronutrient deficiencies and should be particularly paid attention (Maggini et al., 2018). The various aspects of the administration of micronutrient supplements in hospitalized COVID-19 patients are presented in Table 2.

**Vitamin A.** Vitamin A, a fat-soluble vitamin, is vital in immune system function as well as the lung epithelium (Zhang et al., 2018). Clinical and subclinical vitamin A deficiency is considered a major trace elements-related disorder (Tian et al., 2020; Zhang et al., 2018). Vitamin A

**Table 1.** Calorie intake recommendations based on hospitalization stage and nutritional status of patients.

	Hospitalization stage			
		Acute early phase	Acute late phase (ICU day 3–7)	Recovery phase (ICU>7 days)
Nutritional status of patients	Well-nourished and moderate malnutrition	70% calorie from EN route	EN or PN, depending on the energy intake adequacy	80–100% estimated energy
	Severe malnourished	Gradually to supply almost 50% of target energy along with considering refeeding syndrome	EN or gradually PN, depending on the energy intake adequacy along with considering refeeding syndrome	

supplementation may lead to increased levels of immunoglobulin M (IgM) and immunoglobulin G (IgG) as well as T-Lymphocytes activation; and subsequently, improved immune function (Zhang et al., 2018). Moreover, vitamin A supplementation is associated with decreased pneumonia-induced complications and shorter hospitalization periods (Hu et al., 2018). However, we were unable to locate any studies that looked into the impact of vitamin A supplementation (at dosages higher than the RDA) on inflammatory markers, oxidative stress status, or clinical outcomes in COVID-19 patients.

**Vitamins B.** Thiamine deficiency can potentially be associated with disease severity (Shakoor et al., 2020). Thiamine deficiency is reported in ICUs with clinical manifestation of “refeeding syndrome” which is more probable in severely malnourished patients, diuretics therapy, and continuous renal replacement therapy. This condition is usually abundant with several other biochemical abnormalities especially hypophosphatemia (Collie et al., 2017; Doig et al., 2015). A Higher dose of thiamine administration (300 mg/day IV) in high-risk patients or the refeeding syndrome and a low dose (100 mg/day) in all other ICU admitted patients during the first 48 h is recommended (Amrein et al., 2018). Thiamine supplementation early in the course of COVID-19 symptoms may reduce the potential risk of hypoxia and hospitalization (Shakoor et al., 2020). Riboflavin supplements, which have been shown to reduce infection transmission through blood products and to be effective against the MERS virus, may also be helpful against COVID-19 (Ragan et al., 2020). Niacin may have a role in Nicotine Amid di-Nucleotide synthesis and neutrophil activity, resulting in a reduction in IL-6 and IL-1 $\beta$  in cytokine storm and lowered inflammatory markers in ventilated patients (Liu et al., 2020; Shakoor et al., 2020). Previous studies reported that cardiac and diabetic patients (which are considered as high-risk populations for COVID-19) may experience a vitamin B6 deficiency state. Therefore, pyridoxine deficiency may be associated with the severity of disease, and vitamin B6 supplementation in such patients may reduce pro-inflammatory cytokines as well as improve endothelial integrity

(Desbarats, 2020; Lengyel et al., 2008; Merigliano et al., 2018). Folic acid would be possibly effective in reducing respiratory complications of COVID-19 in the early phase, as well (Kumar and Jena, 2020; Sheybani et al., 2020). Finally, Cobalamin deficiency leads to increased oxidative stress and lactate dehydrogenases levels, and this disorder may deteriorate the COVID-19 patients' clinical condition (Grangé et al., 2015; Sabry et al., 2020; Stipp, 2020; Wolffenbuttel et al., 2019). There is some evidence supporting the hypothesis of vitamin B12 supplementation in higher doses than the RDA to decrease the risk of organ failure and disease severity (dos Santos, 2020; Shakoor et al., 2020).

As aforementioned, vitamin B supplementation may have healthful effects on COVID-19 nutritional management, particularly in the patients consuming hydroxychloroquine. However, there is no definite recommendation on the supplementation with higher doses than the RDA amounts in such patients.

**Vitamin C.** Adequate vitamin C is necessary for optimal immune function. Vitamin C supplementation in respiratory infection and pneumonia is debated in several studies (Gombart et al., 2020; Maggini et al., 2018). But, the treatment effect is not shown in two meta-analysis studies in Cochrane Database, and further study is recommended (Hemila and Chalker, 2013; Hemila and Louhiala, 2013).

A meta-analysis of 1210 patients showed that vitamin C administration with doses of 3–10 gr/day reduced mortality (OR = 0.25,  $p < 0.001$ ) (Wang et al., 2019b). Another meta-analysis showed no mortality effect of vitamin C in 142 critical ill patients, but significant decreased need for vasopressor support (standardized mean difference  $-0.71$ ; 95% confidence interval  $(-1.16$  to  $-0.26)$ ;  $p = 0.002$ ) and duration of mechanical ventilation (standardized mean difference  $-0.5$ ; 95% confidence interval  $(-0.93$  to  $-0.06)$ ;  $p = 0.03$ ) (Zhang and Jatava, 2018). Reduction in ventilation time is more considerable in the patients with the longest ventilation time according to the meta-analysis study of 685 patients. This study showed a 14% decrease in the duration of mechanical ventilation ( $p = 0.0001$ ) and 25% in patients who were ventilated for more than 10 h a day ( $p$

**Table 2.** Different aspects of the therapeutic goals of micronutrient supplements in COVID-19 hospitalized patients.

Micronutrient supplement	Immune system function/ inflammation management	Shortening of hospitalization period/ICU admission	Decreasing of mechanical ventilation duration	Reduction of Mortality	Recommendation
Vitamin A	Zhang et al. (2018) Hu et al. (2018)	Hu et al. (2018)			RDA
Vitamin B	Ragan et al. (2020) Shakoor et al. (2020) Liu et al. (2020) Desbarats (2020) Merigliano et al. (2018) Lengyel et al. (2008) Sabry et al. (2020) Stipp (2020) Wolffenbuttel et al. (2019) Grangé (2008)	Shakoor et al. (2020)	Kumar and Jena (2020) Sheybani et al. (2020) dos Santos (2020) Shakoor et al. (2020)		For thiamine, higher dose as IV in high-risk patients or the refeeding syndrome For B2-B3-B6-B9-B12 as RDA
Vitamin C	Gombart et al. (2020) Maggini et al. (2018)	Jamali Moghadam Siahkali et al. (2021)* Du et al. (2019)	Hemila and Chalker (2020) Zhang and Jatva (2018)	Jamali Moghadam Siahkali et al. (2021)* Wang et al. (2019b) Zhang and Jatva (2018)** Ilie et al. (2020)	RDA However, there is no consensus in studies on dosing <sup>a</sup> and its effect on reducing mortality <sup>b</sup> and ventilation.
Vitamin D	Turubiates-Hernández et al. (2021)	Bassante et al. (2021)** Nogues et al. (2021) Alcala-Diaz et al. (2021) Entrenas Castillo et al. (2020)	Bassante et al. (2021)** Murai et al. (2021)	Alcala-Diaz et al. (2021) Murai et al. (2021)** Entrenas Castillo et al. (2020)**	Although effectiveness of vitamin D in moderate to severe conditions of COVID-19 is uncertain (Stroehlein et al. 2021), the ESPEN guideline recommended a dose of 500,000 IU vitamin D within a week after admission to ICU (Singer et al. 2019)
Potassium					Recommendation for supplementation in a deficiency state <sup>c</sup>
Phosphorus					Recommendation for supplementation in a deficiency state <sup>d</sup>
Magnesium					Recommendation for supplementation in a deficiency state <sup>e</sup>
Zinc			Boudreault et al. (2017)		RDA <sup>f</sup> Although there is inconsistent evidence on the possible beneficial effects of zinc supplementation on clinical outcomes <sup>g</sup> , it is reasonable to assess zinc levels in hospitalized patients individually <sup>h</sup>

(continued)

**Table 2.** (continued)

Micronutrient supplement	Immune system function/ inflammation management	Shortening of hospitalization period/ICU admission	Decreasing of mechanical ventilation duration	Reduction of Mortality	Recommendation
Selenium		Observational studies: Zhang et al. (2020) Moghaddam et al. (2020)		Observational studies: Robberecht et al. (2019) Alehagen et al. (2018) Alehagen et al. (2016)	Unknown <sup>1</sup>

\*The results of the study are different from other studies, <sup>a,b</sup>non-significant trend, <sup>a</sup>JamaliMoghaddamSiahkali et al. (2021), Feyaerts and Luyten (2020), Langlois and Lamontagne (2019), <sup>b</sup>Du et al. (2019), Langlois et al. (2019), Putzu et al. (2019), <sup>c</sup>Alfano et al. (2021), Moreno-Pérez et al. (2020), <sup>d</sup>Yang et al. (2021), Xue et al. (2020), Javdani et al. (2020), Taghizadeh-Hesary and Akbari (2020), Kouhpayeh et al. (2020), <sup>e</sup>Tang et al. (2020), <sup>f</sup>Rajendram et al. (2015), <sup>g</sup>Elke et al. (2019), Lee et al. (2019), Singer et al. (2019), LINKO et al. (2019), Heyland et al. (2011), Heyland et al. (2008), <sup>h</sup>Joachimiak (2021), <sup>i</sup>Hiffler and Rakotoambinina (2020).

<0.0001) (Hemila and Chalker, 2020). Reduction of length of stay (MD = -0.96, 95%CI = -1.21 to -0.70,  $p < 0.0001$ ) and ICU length of stay (MD) = -0.23, 95%CI = -0.29 to -0.16,  $p < 0.0001$ ] are showed in another meta-analysis study of 4420 critically ill patients with no mortality effect (Du et al., 2019). Other systematic reviews which are not focused on the administration dose showed no reduction in mortality after vitamin C supplementation (Langlois et al., 2019; Putzu et al., 2019).

A recent research found that vitamin C levels were undetectable in 90 percent of COVID-19 ARDS patients' blood samples (Chiscano-Camón et al., 2020), which might be a reflection of the disease's heightened demand for vitamin C during the inflammatory storm state. In a randomized clinical trial high dose of vitamin C (6 g/d) was significantly associated with a higher length of stay ( $p = 0.014$ ) and did not improve the length of intensive care unit (ICU) stay, SpO<sub>2</sub> levels at discharge time, and mortality significantly (JamaliMoghadamSiahkali et al., 2021). Although a low dose (0.5–2 g/d) is recommended in the early phase of severe COVID-19, (Feyaerts and Luyten, 2020) further studies are needed with a focus on dose administration to conclude the beneficial effects of high dose vitamin C in critically ill COVID-19 patients.

Systematic review studies show no benefit of the low dose of vitamin C supplementation in critically ill patients (Langlois and Lamontagne, 2019). By these available data, vitamin C is not a proven adjuvant therapy in COVID-19 outpatients, and more study is warranted.

**Vitamin D.** Before SARS-CoV-2 advent, a meta-analysis study showed significant risk reduction in acute respiratory tract infection in the patients who received vitamin D supplementation (Adjusted OR: 0.88,  $p < 0.001$ ) (Martineau et al., 2017), and an updated version of the study confirmed the data and recommended the administration of daily doses of 400–1000 IU vitamin D for up to 12 months to prevent acute respiratory infections (Jolliffe et al., 2021).

Based on the immunomodulatory effect of vitamin D, such as maintaining alveolar permeability as a physical barrier and improving innate and adaptive immune responses to the pathogens, the potential protective role of calciferol in COVID-19 was assumed and strengthened by the detection of negative regulation of the Renin-Angiotensin System in SARS Cov-2 infection while 1–25 (OH) 2 D is reported as an essential suppresser of this pathway (Turrubiates-Hernández et al., 2021). An ecological study showed a negative correlation between mortality and mean 25(OH) D concentration among 20 European countries ( $r = -0.43$ ;  $p = 0.05$ ) (Ilie et al., 2020).

A systematic review and meta-analysis study on 31 observational studies showed a positive non-significant trend among 25(OH) D levels <20 ng/mL and an increased risk of non-invasive ventilation, invasive ventilation, ICU admission, and mortality (Bassatne et al., 2021). A cohort study on 838 hospitalized patients with Covid-19 showed Calcifediol treatment decreased the risk for ICU admission

(OR 0.13;  $p < 0.0001$ ), and mortality rate significantly decreased about 50% ( $p = 0.0001$ ) (Nogues et al., 2021). Another cohort study on 537 hospitalized patients reported the same result. (OR = 0.22;  $p < 0.01$ ) (Alcala-Diaz et al., 2021).

A pilot randomized clinical study with calcifediol treatment for hospitalized patients with COVID-19 has reported the positive effect of vitamin D treatment to reduce all-cause mortality [RR 0.11 (95% CI 0.01 to 2.13)] and significantly lower risk of ICU admission (OR = 0.02;  $p < 0.001$ ) (Entrenas Castillo et al., 2020). While a double-blind, randomized, placebo-controlled trial with a single high dose (200,000 UI) of vitamin D<sub>3</sub> at admission showed a significant decrease in the need for mechanical ventilation [RR 0.52 (95% CI 0.24 to 1.13)] and non-significant reduction in in-hospital mortality [RR 1.49 (95% CI 0.55 to 4.05)] (Murai et al., 2021). However, Stroehlein et al. stated in a COCHRANE live systematic review that the evidence for vitamin D's usefulness in moderate to severe COVID-19 symptoms is inconclusive, and that a more robust investigation is required to conclude (Stroehlein et al., 2021). Therefore, the effects of vitamin D administration are controversial and it is not well-defined in subgroups such as normal or deficient serum levels of vitamin D.

Concerning the safety of routine doses of vitamin D supplementation, and the high prevalence of vitamin D deficiency in chronic diseases such as Diabetes Mellitus, hypertension, and morbid obesity which are all recognized as the most important risk factor for morbidity and mortality in COVID-19 (Griffin et al., 2020), supplementation (2000–4000 UI/day), especially in deficiency conditions, can be recommended. However, higher doses (10,000 UI/day) for a few weeks can be administered to reach the goal of 25(OH) D concentrations above 40–60 ng/mL (Grant et al., 2020). Moreover, ESPEN guideline recommended a dose of 500,000 UI vitamin D within a week after admission to the intensive care unit (Singer et al., 2019).

**Potassium.** Hypokalemia is reported as a common electrolyte imbalance with a prevalence of 30.7–50% among hospitalized patients with COVID-19 because of different conditions such as gastrointestinal symptoms, multiple-pharmacies, renal failure, and calcium or magnesium impairment (Alfano et al., 2021; Moreno-Pérez et al., 2020). Hypokalemia should be considered in COVID-19 patients, and in steady-state cases, serum magnesium levels and calcium should be assessed.

**Phosphorus.** Low serum phosphorus is common in COVID-19 patients (Xue et al., 2020; Yang et al., 2021). Phosphorus deficiency is common in conditions predisposing to severe COVID\_19, such as Diabetes, the elderly, and obesity (Van Kempen and Deixler, 2021).

Javdani et al. reported significant relation between the severity of disease and lower serum levels of phosphorus.

Having phosphorus upper than 4.5 is reported as an indicator for better HRCT signs of disease (OR = 3.71;  $p = 0.017$ ) (Javdani et al., 2020). Another study reported a significantly lower level of phosphorus in severe cases ( $p < 0.010$ ) (Xue et al., 2020). Yang et al. showed that hypophosphatemia in critical COVID-19 patients is more prevalent 15.07 times than in moderate ones (Yang et al., 2021).

COVID-19 in severe conditions is a hyper-inflammatory state which can be a cause of ATP depletion (Taghizadeh-Hesary and Akbari, 2020). Moreover, low phosphorous intake in the disease process may occur, and phosphate replacement may improve immunity (Kouhpayeh et al., 2020). Therefore, Phosphor assessment is recommended in an early stage of the disease in COVID-19 patients at risk of deficiency and hospitalized patients, especially in COVID-19 severe cases. Supplementation should be considered in a deficiency state, and special consideration should be taken in the patients with a higher risk of "refeeding syndrome" (Krzak et al., 2011).

**Magnesium.** As reported by previous studies, Magnesium supplementation would be effective in the prevention and/or treatment of respiratory system disorders as well as gastrointestinal tract diseases. In individuals with COVID-19, blood magnesium levels should be examined, especially in those who have been diagnosed with hypertension, renal impairment, or diabetes. As a result, magnesium supplementation in deficient individuals should be explored (Tang et al., 2020).

**Zinc.** Zinc is a micronutrient playing a role in innate and adaptive immunity (Hojo and Fukada, 2016). Previous studies showed that zinc supplementation would reduce the duration of common cold disease (Eby et al., 1984; Hemila et al., 2016; Read et al., 2019). Furthermore, zinc supplementation shortened the duration of sneezing by 22% (−1% to 45%), sore throat by 18% (−10% to 46%), cough by 46% (28% to 64%), muscle ache by 54% (18% to 89%) with no significant effect on fever (Read et al., 2019).

Zinc as an immunomodulatory trace element may be beneficial in critical illnesses as well. Low plasma concentrations of zinc and increased urinary zinc loss have occurred in critically ill states (Cirino Ruocco et al., 2018). A prevalence of being up to 96% is reported for zinc deficiency in acute respiratory distress syndrome (ARDS) patients (Linko et al., 2011). Moreover, zinc deficiency is an independent predisposing factor for mechanical ventilator-induced lung injury exacerbation (Boudreaux et al., 2017). However, there is inconsistent evidence on the possible beneficial effects of zinc supplementation on clinical outcomes in such situations (Elke et al., 2019; Heyland et al., 2008; Lee et al., 2019; Linko et al., 2011; Singer et al., 2019). These controversies could be solved by further investigations about dose, duration, time of administration, and conditions of patients. Regarding the role of zinc in different metabolic pathways, zinc should

be provided, at least in available RDA doses in such patients (Rajendram et al., 2015).

COVID-19 patients experience zinc deficiency states at higher rates than the healthy population (Jothimani et al., 2020). One clinical trial study showed no benefit of reduction in symptoms and outcomes in COVID-19 outpatients by 50 mg of zinc gluconate administration (Thomas et al., 2021). More studies investigating the effects of zinc supplementation on various biochemical indices as well as clinical outcomes in COVID-19 patients, but there are no published results to this moment we are writing the paper (Carlucci et al., 2020). Considering different therapeutic strategies in acute/chronic zinc deficiency disorders, an individualized assessment of zinc status in all hospitalized patients would be reasonable (Joachimiak, 2021).

In COVID-19 patients, there is no data supporting the specific indications and dosage of zinc supplementation. Therefore, all COVID-19 patients should get at least RDA quantities of zinc in their medical nutrition therapy, and nutritionists should decide on higher doses of zinc supplementation based on the patient's clinical state and disease stage.

**Selenium.** According to our searches, no interventional studies were published on the effect of selenium supplementation on the incidence rate, inflammatory indices, or clinical outcomes of COVID-19 disease. However, observational studies reported that lower concentrations of serum selenium were associated with decreased recovery rate in COVID-19 patients (Moghaddam et al., 2020; Zhang et al., 2020). Low serum selenium levels in the elderly are associated with decreased survival and a higher mortality rate (Alehagen et al., 2016, 2018; Robberecht et al., 2019). Therefore, assessment of serum selenium concentrations in all hospitalized patients and appropriate supplement administration in documented deficiencies at any stage of disease would be beneficial. Furthermore, it seems that selenium administration at the beginning of hospitalization or the earliest opportunity before the incidence of cytokine storm would be more efficient (Ersöz et al., 2003). However, the exact indications and recommended dose of selenium supplementation to minimize COVID-19 related complications and comorbidities are unknown (Hiffler and Rakotoambinina, 2020).

A significant drawback of our narrative evaluation was the lack of published studies and information concerning the COVID-19 and nutritional management elements. To study the appliance, further research is needed, including experimental studies and clinical trials.

## Conclusion

Medical nutrition therapy (MNT) for COVID-19 hospitalized patients is considered a critical component of their medical management. Early nutrition support following hemodynamic stability should be regarded in such patients. EN would be the preferred feeding route. Energy and



macronutrients should be provided concerning the past medical history, clinical manifestations, and disease severity of patients. Some potentially recommended micronutrient supplementations should be administered in particular indications.

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### Authors' contributions

The authors' responsibilities were as follows: FR, MP, and SA: designed the research and conducted the library search, and wrote the manuscript; ES designed table and edited the manuscript. All of the authors read and approved the final manuscript.

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### References

- Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R, et al. (2021) Calcifediol treatment and hospital mortality due to COVID-19: a cohort study. *Nutrients* 13: 1760.
- Alehagen U, Aaseth J, Alexander J, et al. (2018) Still reduced cardiovascular mortality 12 years after supplementation with selenium and coenzyme Q10 for four years: a validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly. *PLoS One* 13: e0193120.
- Alehagen U, Johansson P, Björnstedt M, et al. (2016) Relatively high mortality risk in elderly Swedish subjects with low selenium status. *European Journal of Clinical Nutrition* 70: 91–96.
- Alfano G, Ferrari A, Fontana F, et al. (2021) Hypokalemia in patients with COVID-19. *Clinical and Experimental Nephrology* 25(4): 401–409.
- Aman F and Masood S (2020) How nutrition can help to fight against COVID-19 pandemic. *Pakistan Journal of Medical Sciences* 36: S121–S123.
- Amrein K, Oudemans-van Straaten HM and Berger MM (2018) Vitamin therapy in critically ill patients: focus on thiamine, vitamin C, and vitamin D. *Intensive Care Medicine* 44: 1940–1944.
- Bassatne A, Basbous M, Chakhtoura M, et al. (2021) The link between COVID-19 and Vitamin D (VIVID): A systematic review and meta-analysis. *Metabolism: Clinical and Experimental* 119: 154753.
- Boudreaux F, Pinilla-Vera M, Englert JA, et al. (2017) Zinc deficiency primes the lung for ventilator-induced injury. *JCI Insight* 2. doi:10.1172/jci.insight.86507
- Carlucci PM, Ahuja T, Petrilli C, et al. (2020) Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *Journal of Medical Microbiology* 69: 1228–1234.
- Casaer MP and Bellomo R (2019) Micronutrient deficiency in critical illness: an invisible foe? *Intensive Care Medicine* 45: 1136–1139.
- Charoenngam N, Shirvani A, Reddy N, et al. (2021) Association of vitamin D status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. *Endocrine Practice* 27(4): 271–278.
- Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, et al. (2020) Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Critical Care* 24: 22.
- Cirino Ruocco MA, Pacheco Cechinatti ED, Barbosa F, et al. (2018) Zinc and selenium status in critically ill patients according to severity stratification. *Nutrition (Burbank, Los Angeles County, Calif.)* 45: 85–89.
- Collie JTB, Greaves RF, Jones OAH, et al. (2017) Vitamin B1 in critically ill patients: needs and challenges. *Clinical Chemistry and Laboratory Medicine* 55: 1652–1668.
- Cortegiani A, Ingoglia G, Ippolito M, et al. (2020) A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *Journal of Critical Care* 57: 279–283.
- Desbarats J (2020) Pyridoxal 5'-phosphate to mitigate immune dysregulation and coagulopathy in COVID-19.
- De Waele E, Jakubowski JR, Stocker R, et al. (2021) Review of evolution and current status of protein requirements and provision in acute illness and critical care. *Clinical Nutrition* 40: 2958–2973.
- Doig GS, Simpson F, Heighes PT, et al. (2015) 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. *The Lancet Respiratory Medicine* 3: 943–952.
- Dos Santos LMJ (2020) Can vitamin B12 be an adjuvant to COVID-19 treatment? *GSC Biological and Pharmaceutical Sciences* 11: 001–005.
- Du X, Yang C and Yu X (2019) [Effect of vitamin C on prognosis of critically ill patients: a meta-analysis]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 31: 942–948.
- Eby GA, Davis DR and Halcomb WW (1984) Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. *Antimicrobial Agents and Chemotherapy* 25: 20–24.
- Elke G, Hartl WH, Kreymann KG, et al. (2019) Clinical nutrition in critical care medicine – guideline of the German society for

- nutritional medicine (DGEM). *Clinical Nutrition ESPEN* 33: 220–275.
- Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. (2020) Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. *The Journal of Steroid Biochemistry and Molecular Biology* 203: 105751.
- Ersöz G, Yakaryılmaz A and Turan B (2003) Effect of sodium selenite treatment on platelet aggregation of streptozotocin-induced diabetic rats. *Thrombosis Research* 111: 363–367.
- Feyaerts AF and Luyten W (2020) Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? *Nutrition (Burbank, Los Angeles County, Calif.)* 79-80: 110948.
- Gombart AF, Pierre A and Maggini S (2020) A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. *Nutrients* 12: 36.
- Grangé S, Bekri S, Artaud-Macari E, et al. (2015) Adult-onset renal thrombotic microangiopathy and pulmonary arterial hypertension in cobalamin C deficiency. *The Lancet* 386: 1011–1012.
- Grant WB, Lahore H, McDonnell SL, et al. (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 12: 88.
- Griffin G, Hewison M, Hopkin J, et al. (2020) Vitamin D and COVID-19: evidence and recommendations for supplementation. *Royal Society Open Science* 7: 201912.
- Hemila H and Chalker E (2013) Vitamin C for preventing and treating the common cold. *Cochrane Database of Systematic Reviews* 2013: Cd000980.
- Hemila H and Chalker E (2020) Vitamin C may reduce the duration of mechanical ventilation in critically ill patients: a meta-regression analysis. *Journal of Intensive Care* 8: 15.
- Hemila H and Louhiala P (2013) Vitamin C for preventing and treating pneumonia. *Cochrane Database of Systematic Reviews*: Cd005532. doi:10.1002/14651858.CD005532.pub3
- Hemila H, Petrus EJ, Fitzgerald JT, et al. (2016) Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis. *British Journal of Clinical Pharmacology* 82: 1393–1398.
- Heyland DK, Jones N, Cvijanovich NZ, et al. (2008) Zinc supplementation in critically ill patients: a key pharmacnutrient? *Journal of Parenteral and Enteral Nutrition* 32: 509–519.
- Hiffler L and Rakotoambinina B (2020) Selenium and RNA virus interactions: potential implications for SARS-CoV-2 infection (COVID-19). *Frontiers in Nutrition* 7. doi:10.3389/fnut.2020.00164
- Hojyo S and Fukada T (2016) Roles of zinc signaling in the immune system. *Journal of Immunology Research* 2016: 1–21.
- Hu N, Li Q-B and Zou S-Y (2018) Effect of vitamin A as an adjuvant therapy for pneumonia in children: a meta analysis. *Zhongguo Dang dai er ke za zhi=Chinese Journal of Contemporary Pediatrics* 20: 146–153.
- Huang C, Wang Y, Li X, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 395: 497–506.
- Ilie PC, Stefanescu S and Smith L (2020) The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clinical and Experimental Research* 32: 1195–1198.
- JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, et al. (2021) Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. *European Journal of Medical Research* 26: 20.
- Javdani F, Parsa S, Shakeri H, et al. (2020) Phosphate levels and pulmonary damage in COVID-19 patients based on CO-RADS scheme: is there any link between parathyroid gland and COVID-19? *medRxiv*: 2020.2008.2025.20181453.
- Jin Y-H, Cai L, Cheng Z-S, et al. (2020) A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Military Medical Research* 7: 4.
- Joachimiak MP (2021) Zinc against COVID-19? Symptom surveillance and deficiency risk groups. *PLoS Neglected Tropical Diseases* 15: e0008895–e0008895.
- Jolliffe DA, Camargo CA Jr., Sluyter JD, et al. (2021) Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *The Lancet Diabetes & Endocrinology* 9: 276–292.
- Jothimani D, Kailasam E, Danielraj S, et al. (2020) COVID-19: poor outcomes in patients with zinc deficiency. *International Journal of Infectious Diseases* 100: 343–349.
- Katona P and Katona-Apte J (2008) The interaction between nutrition and infection. *Clinical Infectious Diseases* 46: 1582–1588.
- Khayyatzadeh SS (2020) Nutrition and infection with COVID-19. *Journal of Nutrition and Food Security* 5: 93–96.
- Kouhpayeh S, Shariati L, Boshtam M, et al. (2020) The molecular story of COVID-19; NAD+depletion addresses all questions in this infection.
- Krzak A, Pleva M and Napolitano LM (2011) Nutrition therapy for ALI and ARDS. *Critical Care Clinics* 27: 647–659.
- Kumar V and Jena M (2020) In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19. *VirusDisease* 32: 29–37.
- Lambell KJ, Tatucu-Babet OA, Chapple LA, et al. (2020) Nutrition therapy in critical illness: a review of the literature for clinicians. *Critical Care* 24: 35.
- Langlois PL and Lamontagne F (2019) Vitamin C for the critically ill: is the evidence strong enough? *Nutrition (Burbank, Los Angeles County, Calif.)* 60: 185–190.
- Langlois PL, Manzanares W, Adhikari NKJ, et al. (2019) Vitamin C administration to the critically ill: a systematic review and meta-analysis. *Journal of Parenteral and Enteral Nutrition* 43: 335–346.
- Lee YH, Bang E-S, Lee J-H, et al. (2019) Serum concentrations of trace elements zinc, copper, selenium, and manganese in critically ill patients. *Biological Trace Element Research* 188: 316–325.
- Lengyel CO, Whiting SJ and Zello GA (2008) Nutrient inadequacies among elderly residents of long-term care facilities. *Canadian Journal of Dietetic Practice and Research* 69: 82–88.
- Linko R, Karlsson S, Pettilä V, et al. (2011) Serum zinc in critically ill adult patients with acute respiratory failure. *Acta Anaesthesiologica Scandinavica* 55: 615–621.
- Liu B, Li M, Zhou Z, et al. (2020) Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *Journal of Autoimmunity* 111: 102452.
- Maggini S, Pierre A and Calder PC (2018) Immune function and micronutrient requirements change over the life course. *Nutrients* 10: 1531.

- Martineau AR, Jolliffe DA, Hooper RL, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *Bmj* 356: i6583.
- McClave SA, Taylor BE, Martindale RG, et al. (2016) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (A.S.P.E.N.). *Journal of Parenteral and Enteral Nutrition* 40: 159–211.
- McMillan DC, Maguire D and Talwar D (2019) Relationship between nutritional status and the systemic inflammatory response: micronutrients. *Proceedings of the Nutrition Society* 78(1): 56–67.
- Medeiros de Moraes C (2021) Nutritional therapy in COVID-19 management. *Kompass Nutrition & Dietetics* 1: 10–12.
- Mendes A, Serratrice C, Herrmann FR, et al. (2021) Nutritional risk at hospital admission is associated with prolonged length of hospital stay in old patients with COVID-19. *Clinical Nutrition*. doi:10.1016/j.clnu.2021.03.017
- Merigliano C, Mascolo E, Burla R, et al. (2018) The relationship between vitamin B6, diabetes and cancer. *Frontiers in Genetics* 9: 88.
- Moghaddam A, Heller RA, Sun Q, et al. (2020) Selenium deficiency is associated with mortality risk from COVID-19. *Nutrients* 12: 2098.
- Moreno-Pérez O, Leon-Ramirez JM, Fuertes-Kenneally L, et al. (2020) Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: a case series of 306 Mediterranean patients. *International Journal of Infectious Diseases* 100: 449–454.
- Murai IH, Fernandes AL, Sales LP, et al. (2021) Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. *JAMA* 325: 1053–1060.
- Nogues X, Ovejero D, Pineda-Moncusí M, et al. (2021) Calcifediol treatment and COVID-19-related outcomes. *The Journal of Clinical Endocrinology & Metabolism* 106: e4017–e4027.
- Pratt PC, Vollmer RT, Shelburne JD, et al. (1979) Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. I. Light microscopy. *The American Journal of Pathology* 95(1): 191.
- Putzu A, Daems AM, Lopez-Delgado JC, et al. (2019) The effect of vitamin C on clinical outcome in critically ill patients: a systematic review with meta-analysis of randomized controlled trials. *Critical Care Medicine* 47: 774–783.
- Ragan I, Hartson L, Pidcoke H, et al. (2020) Pathogen reduction of SARS-CoV-2 virus in plasma and whole blood using riboflavin and UV light. *PLoS One* 15: e0233947.
- Rajendram R, Preedy VR and Patel VB (eds.) (2015) *Diet and Nutrition in Critical Care*. Springer. New York
- Read SA, Obeid S, Ahlenstiel C, et al. (2019) The role of zinc in antiviral immunity. *Advances in Nutrition* 10: 696–710.
- Reintam Blaser A, Jakob SM and Starkopf J (2016) Gastrointestinal failure in the ICU. *Current Opinion in Critical Care* 22(2): 128–141.
- Rice TW (2012) Enteral Omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury (vol 306, pg 1574, 2011). *Jama-Journal of the American Medical Association* 307(6): 563–563.
- Robberecht H, De Bruyne T, Davioud-Charvet E, et al. (2019) Selenium status in elderly people: longevity and age-related diseases. *Current Pharmaceutical Design* 25: 1694–1706.
- Sabry W, Elemary M, Burnouf T, et al. (2020) Vitamin B12 deficiency and metabolism-mediated thrombotic microangiopathy (MM-TMA). *Transfusion and Apheresis Science* 59: 102717.
- Shakoor H, Feehan J, Mikkelsen K, et al. (2020) Be well: a potential role for vitamin B in COVID-19. *Maturitas* 144: 108–111.
- Sheybani Z, Dokoohaki MH, Negahdaripour M, et al. (2020) The role of folic acid in the management of respiratory disease caused by COVID-19.
- Singer P, Blaser AR, Berger MM, et al. (2019) ESPEN Guideline on clinical nutrition in the intensive care unit. *Clinical Nutrition* 38: 48–79.
- Stipp MM (2020) SARS-CoV-2: micronutrient optimization in supporting host immunocompetence. *International Journal of Clinical Case Reports and Reviews* 2: 01–01.
- Stroehlein JK, Wallqvist J, Iannizzi C, et al. (2021) Vitamin D supplementation for the treatment of COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 5: Cd015043.
- Taghizadeh-Hesary F and Akbari H (2020) The powerful immune system against powerful COVID-19: A hypothesis. *Medical Hypotheses* 140: 109762.
- Tang C-F, Ding H, Jiao R-Q, et al. (2020) Possibility of magnesium supplementation for supportive treatment in patients with COVID-19. *European Journal of Pharmacology* 886: 173546.
- Thomas S, Patel D, Bittel B, et al. (2021) Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. *JAMA Network Open* 4: e210369.
- Tian Y, Tian Q, Wu Y, et al. (2020) Vitamin A supplement after neonatal Streptococcus pneumoniae pneumonia inhibits the progression of experimental asthma by altering CD4+T cell subsets. *Scientific Reports* 10: 1–10.
- Turrubiates-Hernández FJ, Sánchez-Zuno GA, González-Estevez G, et al. (2021) Potential immunomodulatory effects of vitamin D in the prevention of severe coronavirus disease 2019: an ally for Latin America (review). *International Journal of Molecular Medicine* 47. doi:10.3892/ijmm.2021.4865
- Van Kempen TATG and Deixler E (2021) SARS-CoV-2: influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19. *American Journal of Physiology-Endocrinology and Metabolism* 320: E2–E6.
- Wang MX, Koh J and Pang J (2019a) Association between micronutrient deficiency and acute respiratory infections in healthy adults: a systematic review of observational studies. *Nutrition Journal* 18(1): 1–12.
- Wang Y, Lin H, Lin BW, et al. (2019b) Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. *Annals of Intensive Care* 9: 58.
- Wolffenbutterl BH, Wouters HJ, Heiner-Fokkema MR, et al. (2019) The many faces of cobalamin (vitamin B12) deficiency. *Mayo Clinic Proceedings: Innovations, Quality & Outcomes* 3: 200–214.
- World Health Organization (2020a) WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet] [cited 2020 Mar 11]. Geneva (Switzerland): World Health Organization.

- World Health Organization (2020b) Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020 (No. WHO/2019-nCoV/clinical/2020.4). World Health Organization
- Xue X, Ma J, Zhao Y, et al. (2020) Correlation between hypophosphatemia and the severity of Corona Virus Disease 2019 patients. *medRxiv*: 2020.2003.2027.20040816.
- Yang C, Ma X, Wu J, et al. (2021) Low serum calcium and phosphorus and their clinical performance in detecting COVID-19 patients. *Journal of Medical Virology* 93: 1639–1651.
- Zhang J, Taylor EW, Bennett K, et al. (2020) Association between regional selenium status and reported outcome of COVID-19 cases in China. *The American Journal of Clinical Nutrition* 111: 1297–1299.
- Zhang M and Jatava DF (2018) Vitamin C supplementation in the critically ill: a systematic review and meta-analysis. *SAGE Open Medicine* 6: 2050312118807615.
- Zhang P, Cui T, Zhang Z, et al. (2018) Low-dose vitamin A therapy on T lymphocyte function in neonatal pneumonia. *European Review for Medical and Pharmacological Sciences* 22: 4371–4374.