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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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REVIEW

Metabolic and nutritional triggers associated with increased risk of liver complications in SARS-CoV-2

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Abstract

Obesity, diabetes, cardiovascular and respiratory diseases, cancer and smoking are risk factors for negative outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can quickly induce severe respiratory failure in 5% of cases. Coronavirus disease-associated liver injury may occur during progression of SARS-CoV-2 in patients with or without pre-existing liver disease, and damage to the liver parenchyma can be caused by infection of hepatocytes. Cirrhosis patients may be particularly vulnerable to SARS-CoV-2 if suffering with cirrhosis-associated immune dysfunction. Furthermore, pharmacotherapies including macrolide or quinolone antibiotics and steroids can also induce liver damage. In this review we addressed nutritional status and nutritional interventions in severe SARS-CoV-2 liver patients. As guidelines for SARS-CoV-2 in intensive care (IC) specifically are not yet available, strategies for management of sepsis and SARS are suggested in SARS-CoV-2. Early enteral nutrition (EN) should be started soon after IC admission, preferably employing iso-osmolar

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polymeric formula with initial protein content at 0.8 g/kg per day progressively increasing up to 1.3 g/kg per day and enriched with fish oil at 0.1 g/kg per day to 0.2 g/kg per day. Monitoring is necessary to identify signs of intolerance, hemodynamic instability and metabolic disorders, and transition to parenteral nutrition should not be delayed when energy and protein targets cannot be met *via* EN. Nutrients including vitamins A, C, D, E, B6, B12, folic acid, zinc, selenium and ω-3 fatty acids have in isolation or in combination shown beneficial effects upon immune function and inflammation modulation. Cautious and monitored supplementation up to upper limits may be beneficial in management strategies for SARS-CoV-2 liver patients.

Key Words: COVID-19; SARS-CoV-2; Enteral nutrition; Parenteral nutrition; Hepatic failure

Core Tip: Coronavirus disease-associated liver injury may occur in the progression of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with or without pre-existing liver disease. Patients with cirrhosis-associated immune dysfunction are particularly vulnerable. Strategies for management of sepsis and SARS are suggested in SARS-CoV-2 for intensive care patients, including early enteral nutrition soon after intensive care unit admission. Transition to parenteral nutrition should not be delayed when energy and protein targets cannot be met *via* EN. In outpatient settings, micronutrient and ω-3 fatty acids have shown beneficial effects upon immune function and inflammation modulation and may be beneficial in management for SARS-CoV-2 liver patients.

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INTRODUCTION

In December 2019 a new viral infection was identified and observed to quickly induce severe respiratory failure. Its aetiological agent was described as a new beta-coronavirus, responsible for inducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), distinct from SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The disease spread extremely quickly around the globe, and the World Health Organization declared in March 2020 a pandemic[1]. It is believed that the SARS-CoV-2 may have mutated in wild sources including bats and snakes, and passed onto humans through direct contact, including their consumption, or indirect contact, for example exposure to faeces[1]. Anthroponotic transmission occurs mainly through saliva droplets, aerosols and through direct or close physical contact. Measures aimed at blocking droplets and aerosols such as efficient face covering, social distancing and hand and surface cleaning are imperative in reducing transmission[2].

Recent studies have described the angiotensin-converting enzyme receptor (ECA2) as a gateway for viral penetration into the host cells[3]. The ECA2 receptor is abundant in lung alveolar cells, which explains the significant pulmonary component of this infection. The gastrointestinal tract, heart and blood vessels are also target organs[4].

Around 81% of patients with coronavirus disease 2019 (COVID-19) infection will develop mild or mild to moderate disease. However, a study examining over 70000 cases in China showed that evolution to more severe forms is prone to occur in the elderly and in individuals suffering with comorbidities, such as systemic arterial hypertension, type 2 diabetes mellitus, heart disease, obesity, smoking, chronic pulmonary disease and cancer. Children are not statistically present as a risk group[5], and the male gender may be a potential risk factor[6]. Severe cases will account for

approximately 14% of infected patients, who often need mechanical ventilation and present high mortality rates, reaching 80% within the severe case category. The overall risk of mortality in the general population varies from less than 1% to 3%[7].

CLINICAL AND HEPATOLOGICAL ASPECTS OF SARS-COV-2

A recent study recruiting 745 patients suffering with chronic liver disease and diagnosed with SARS-CoV-2 showed that cirrhosis was strongly associated with worsened outcomes, and of the 150 patients who died during the study, 82% had a diagnosis of cirrhosis. Although in that study the most common cause of death was infection-associated lung injury, and in only 19% of cases the primary cause of death was liver failure, such findings suggest that cirrhosis and its consequent immune dysfunction are potential facilitators of lung injury[8].

Hyperglycaemia, a metabolic disarrangement observed not only in type 2 diabetes but also in other conditions characterized by an important pro-inflammatory background, such as cardiovascular disease, hepatic steatosis, cancer and chronic respiratory disease, including respiratory disease induced by smoking, is known to impair the immune response and consequently lead to a worsened clinical evolution in SARS-CoV-2 patients[9]. Hyperglycaemia is a common feature of severe SARS-CoV-2 infection, usually induced by glucocorticoid hypersecretion associated with metabolic stress, and manifested in approximately 51% of cases[10]. The hyperglycaemia observed in severe cases has also been associated with transient impairment of pancreatic islet cell function[11]. Hyperglycaemia should not be neglected in SARS-CoV-2 therapies as it can induce additional immune suppression.

The presence of metabolic disturbances, inflammation and exacerbated oxidative stress are features associated with a rapid clinical deterioration in SARS. Although all populational groups can be affected by the viral disease, the elderly and patients with underlying clinical conditions, especially obesity and type 2 diabetes mellitus, are more vulnerable and are at greater risk of developing the more severe forms of SARS-CoV-2[12].

Individuals with obesity present a range of metabolic disturbances that facilitate worsened clinical outcomes, including alterations in different stages of their innate and adaptive immune response, a state of mild chronic inflammation, chronically higher levels of pro-inflammatory adipokines and lower levels of anti-inflammatory adipokines, and a strong association with type 2 diabetes. It is known that such unfavourable biochemical environment contributes to immune dysregulation and has been described as an important determinant in the severity of viral influenza infection [13,14]. Chronic inflammation associated with obesity jeopardizes macrophage activation by antigen presentation and pro-inflammatory cytokine synthesis[13]. In addition, B and T cell response are attenuated in obesity, contributing to increased susceptibility and delayed resolution of viral infection[13,15]. A recent study that examined the medical records of 37121 patients diagnosed with SARS-CoV-2 showed that age, the male gender and body mass index were unadjusted risk factors for disease severity[16].

A meta-analysis covering 46248 patients and examining the prevalence of comorbidities and underlying diseases in SARS-CoV-2 patients showed that the most prevalent comorbidities were arterial hypertension (17%), diabetes (8%), cardiovascular diseases (5%) and diseases of the respiratory tract (2%). Statistical analysis of each subgroup demonstrated that the presence of comorbidities in SARS-CoV-2 patients may increase the risk for greater severity and unfavourable clinical outcomes[17]. A diagnosis of diabetes was associated with a more severe clinical evolution (19.3%) when compared to non-diabetic individuals (11%) in severe case patients. The worsened clinical evolution cases showed more comorbidities including chronic obstructive pulmonary disease (4.8%), coronary heart disease (10.4%) and hypertension (38.7%). It has also been shown that hyperglycaemia at SARS-CoV-2 admission was associated with more severe evolution and higher mortality[18].

Some clinical and observational studies have described a “cytokine storm” in SARS-CoV-2 infection, which is characterised by significantly exacerbated systemic inflammation and immune dysfunction[19,20]. A study found that the pro-inflammatory cytokines related to macrophage function, mainly interleukin (IL) 6, IL-10 and tumour necrosis factor-α, increase significantly in most severe cases, in relation to cases of lesser intensity. Meanwhile, IL-6 levels remain high even in patients who have had moderate SARS-CoV-2 infection[19].

A meta-analysis evaluated clinical data obtained from 10 studies with 1995 cases in total and found that the immunological response of the patients included in the study was consistent with viral respiratory tract infection: 64.5% of patients showed lymphocytopenia, 29.4% leukocytopenia, 44.3% increased C reactive protein (CRP) and 28.3% showed increased lactate dehydrogenase (LDH)[20]. Furthermore, patients with more severe clinical presentation showed on hospital admission significantly increased inflammatory markers including CRP, ferritin, alanine aminotransaminase (ALT), aspartate aminotransferase (AST), LDH, gamma-glutamyl transferase (gamma-GT), as well as hypoalbuminemia, lymphocytopenia, neutropenia and eosinopenia[19-21].

Patients with chronic liver disease, particularly cirrhosis, show multiple mechanisms of immune dysfunction that together can increase the vulnerability to infection and an inadequate inflammatory response, defined as cirrhosis-associated immune dysfunction[22,23]. Elevation of transaminases and other biomarkers of liver dysfunction are common in SARS-CoV-2 patients, occurring in approximately 15% to 65% of cases. Abnormalities in liver biochemistry are commonly observed in SARS-CoV-2 patients regardless of the presence or not of pre-existing liver disease. However, the mechanisms underlying the impact of COVID-19 infection on liver function are not fully understood and may be multifactorial[24,25].

COVID-associated liver injury is defined as any liver injury that occurs in SARS-CoV-2 progression and treatment in patients with or without pre-existing liver disease. Generally, 2% to 11% of SARS-CoV-2 patients show underlying liver disease, and 14% to 53% show elevated AST and ALT[26]. Damage to the liver parenchyma in SARS-CoV-2 patients can be caused directly by infection of liver cells, once the ACE2 protein is expressed in hepatocytes and cholangiocytes[26,27]. Viral binding to ACE2 allows the virus to penetrate hepatocytes, inducing cytokine activation, apoptosis and necrosis, with resulting liver damage[28]. However, in addition to COVID as primary cause of liver disease, it is clinically important to note that pharmacotherapies including macrolide or quinolone antibiotics and steroids can also induce liver damage [29].

A study recruiting 1099 SARS-CoV-2 patients showed that 23.7% of the cohort had some pre-existing liver disease, including hepatitis B infection, non-alcoholic fatty liver disease and alcohol-related liver disease[30]. Hepatitis B was the most prevalent disease, identified in 2.1% of that sample population, with the majority of those patients presenting a more severe SARS-CoV-2 clinical evolution. Other studies have found hepatitis B to be more frequent in male individuals and in patients taking a worsened clinical outcome[26,29,31].

However, a recent retrospective study assessing the clinical presentation and specific biomarkers of 158 hospitalized SARS-CoV-2 patients showed that 42.4% of the cohort had elevated AST, ALT, alkaline phosphatase (AP), gamma-GT and total bilirubin at admission, and that 31.6% of the patients developed liver biomarker abnormalities in the course of their hospitalization. The liver changes were correlated with the oxygenation index, and at the time of discharge 40.5% of the patients were still showing abnormal liver biomarkers. In addition, factors such as younger age, hypertension and lymphocytopenia were independent risk factors for the persistence of abnormal liver markers during hospitalization[32]. A study carried out with 288 patients hospitalized for COVID-19 and previously established chronic liver disease caused mainly by viruses, metabolic fatty liver disease and alcohol intake, showed that from the 43 patients diagnosed with cirrhosis, 57% of them had the disease decompensated at the time of admission for SARS-Cov-2, and that mortality rate was extremely high in those patients, particularly in those with Child-Pugh cirrhosis score of ≥ 9[33].

Patients diagnosed with COVID-19 confirmed by computed tomography during the subclinical phase, that is, before the onset of symptoms, had a significantly lower incidence of AST abnormality than patients diagnosed after the onset of symptoms [34]. In addition, COVID-19 can worsen underlying chronic liver disease, inducing disease decompensation and acutely exacerbated chronic liver failure, a condition associated with high mortality rate. Recently, Cai *et al*[35] proposed a classification for the various typical liver test abnormalities found in SARS-CoV-2 patients. The study defined three patterns of injury based on ALT, AST, gamma-GT, AP and total bilirubin: first category: hepatocellular lesion usually progressing with predominant elevation of AST and ALT; second category: Cholestatic-type lesion with predominantly elevated gamma-GT and AP; and third category: mixed injury associated with an increase in all hepatocellular markers. It was observed that the presence of abnormalities in liver tests at hospital admission significantly increased the risk of severe pneumonia in the studied population, especially among those with hepatocellular or mixed lesions[35].

The SARS-CoV-2 virus was detected by *in situ* hybridization in 68% of liver sample biopsies of 48 patients who died of severe lung disease attributed to the infection[36]. Histological examination also identified abnormalities in intrahepatic vascular structures, mainly portal and sinusoidal microthrombosis (100% of cases), macrovesicular steatosis (50%), mild portal inflammation (66%) and portal fibrosis. The finding of steatosis was predominant in patients with obesity and overweight. The study of Sonzogni *et al*[36] reinforces the hypothesis that disturbances in the coagulation cascade or impaired blood circulation or endothelial damage may trigger mechanisms in the pathogenesis of COVID-19 damage in the liver.

NUTRITION AND CHRONIC LIVER DISEASE IN THE CONTEXT OF SARS-COV-2

Chronic consumption of westernised diets (WD), which typically contain high levels of saturated fats and simple carbohydrates, contributes to the incidence of obesity and type II diabetes, which are conditions positively associated with the more severe forms of SARS-CoV-2 infection and higher mortality rate[37]. WD chronic consumption activates the innate immune system and compromises adaptive immunity, leading to chronic inflammation and impaired host immune defence against the virus[12]. In addition to impaired innate immunity, WD chronic consumption is known to inhibit T and B function in the adaptive immune system, potentially *via* increased oxidative stress[12,38].

WD are also associated with intestinal dysbiosis and unbalanced pro/anti-inflammatory-associated T function in the intestine, with consequent immune incompetence, intestinal and extra-intestinal inflammation. The immune imbalance resulted from gut dysbiosis can worsen infectious conditions and dysregulate metabolic pathways, increasing the risk for liver complications[37,39-41].

A study evaluated a dataset from 188 countries to identify effects of diet, malnutrition and obesity upon the global SARS-CoV-2 cases and their underlying circumstances, as well as mortality and recovery rates[40]. The results suggest that populations that consume predominantly WD showed higher SARS-CoV-2-associated mortality. Such findings may be explained by the disturbances induced by WD upon intestinal microbiota, affecting the phenotype and function of intestinal T CD4+ cells, which can result in greater susceptibility to infections[41].

In summary, individuals suffering with systemic inflammation induced by overweight or obesity and associated chronic diseases such as diabetes, heart, kidney, liver and lung diseases, are more likely to develop the most severe forms of SARS-CoV-2. Therefore, a broader access to nutritional knowledge to the wider population, with the subsequent adoption of healthier eating behaviours, are Public Health priorities. Populations in general need to be made aware that healthier eating behaviours are important protective factors against long-term complications and negative outcomes in SARS-CoV-2[12]. In general, nutritional recommendations ought to focus on reduction of saturated fats and simple sugars, combined with the adequate consumption of dietary fibre, whole grains, polyunsaturated fats, and antioxidant and bioactive nutrients that enhance immune function[12,42]. Figure 1 illustrates the main factors associated with the pathophysiology of SARS-CoV-2 disease that contribute to the most severe forms of the infection.

NUTRITIONAL THERAPIES FOR PATIENTS WITH LIVER COMPLICATIONS

Nutritional therapy (NT) recommendations for critically ill patients with a diagnosis of acute liver failure (ALC) or acute-on-chronic liver failure (ACLF) follow the same principles as NT aimed at critically ill patients. Early enteral nutrition (EN) is recommended, starting with trophic rates (10 mL/h to 20 mL/h) containing approximately 15 kcal/kg BW per day to 20 kcal/kg BW per day, due to increased risk of diet intolerance secondary to mesenteric ischaemia, vomiting, or adynamic ileus, which may occur during the first week of hospitalization[43]. Energy content can be gradually increased up until reaching 30 kcal/kg BW per day to 35 kcal/kg BW per day[44]. In severely ill ALC or ACLF patients who are malnourished, EN alone or associated with parenteral nutrition (PN) should be started immediately[44]. The enteral route should be preferred whenever possible, but PN should be initiated if there is a need to reach nutritional requirements, especially when EN is not safe or

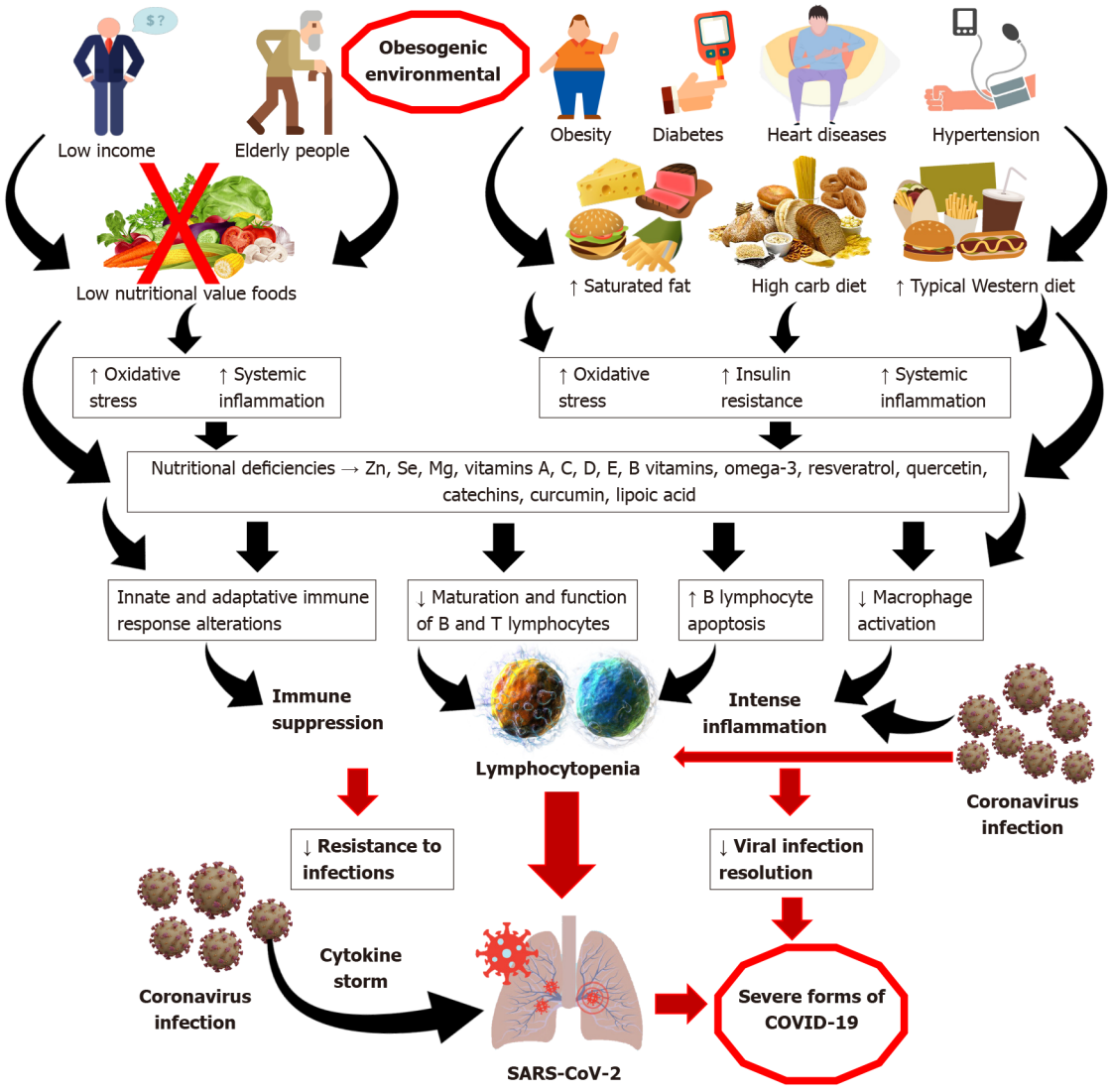

Figure 1 Health, diet and lifestyle practices associated with clinical outcomes in SARS-CoV-2 infection. Individuals suffering with systemic inflammatory background associated with overweight, obesity, diabetes, heart disease and hypertension, and chronic liver disease, as well as elderly individuals, are more susceptible to develop the most severe forms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Chronic consumption of typical westernised diets (WD) diets, which are rich in saturated fat, carbohydrates with high glycaemic index, and low in fresh fruits and vegetables, is relatively common amongst individuals who present worsened clinical outcomes. A typical WD dietary pattern features low nutritional value, facilitating deficiencies of vitamins, minerals, polyunsaturated fatty acids and bioactive compounds such as resveratrol, quercetin, catechins, curcumin and lipoic acid, amongst others. Nutritional deficit can facilitate the exacerbation of oxidative stress, inflammation and insulin resistance, with consequent disturbances in the innate and adaptive immune response, resulting in suppression of the immune response and greater susceptibility to infections. Coronavirus infection is usually associated with a "cytokine storm", intense inflammation, leukopenia and lymphocytopenia. Individuals with preestablished pro-inflammatory background and impaired immune system due to poor diet are at greater risk of evolving more rapidly to the more severe forms of SARS-CoV-2 infection[12,37,81]. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

tolerated[43,44,45].

Continuous EN is recommended over bolus infusion to reduce the incidence of diarrhoea, improve glycaemic control, and reduce healthcare worker interaction, thereby limiting their exposure to SARS-CoV-2[43]. A daily prescription of 1.2 g protein/kg BW is recommended for patients with liver disease without malnutrition, and 1.5 g of protein for malnourished or sarcopenic patients. However, in patients with severe hyperacute disease with hepatic encephalopathy and high arterial ammonia, or at risk of developing cerebral oedema, protein nutritional support can be delayed for 24 h to 48 h until the hyperammonaemia is controlled[44]. Additionally, the use of standard formulae may be suggested as no robust scientific evidence appears to be available as yet on the proven benefits of formulae supplemented with branched chain amino acids in critically ill patients with liver disease[44,45].

NUTRITIONAL THERAPIES FOR SARS-COV-2 PATIENTS WITH LIVER COMPLICATIONS

As NT guidelines for SARS-CoV-2 in intensive care specifically are not yet available, nutrient recommendations are centred on the principles of nutrition in intensive care, which must be adapted to the patient considering their clinical conditions and associated complications. Therefore, as the patient with severe SARS-CoV-2 generally presents manifestations similar to patients admitted to intensive care unit (ICU) with pulmonary impairment, the employment of strategies for the management of conditions such as sepsis and severe acute respiratory distress syndrome is suggested [46].

Decision making regarding the initiation and progression of NT, as well as the selection of the feeding route and the type of diet during hospitalization of moderate and severe SARS-CoV-2 patients, need to consider the patient's clinical presentation [47]. EN is less expensive and inherently presents overall lower risks for the patient than PN, in addition to mimicking a more physiological form of feeding. However, both types of nutritional administration can have adverse effects and long-term complications[48]. Early EN shows several benefits including increased splanchnic blood flow, maintained enterocyte barrier and stimulated immunity. Although current evidence suggests that the use of early EN in critically ill patients results in the preservation of splanchnic blood flow, high calorie EN can induce complications in patients with hypovolemic shock. However, it has been shown that EN infusion at low dosage to allow for intestinal trophism is associated with better clinical outcomes in critically ill patients[49].

Thus, it is recommended that EN should be started as soon as possible after admission to ICU, preferably employing an iso-osmolar standard polymeric formula designed for gradual administration, starting with low flow and evolving according to gastrointestinal tolerance. Monitoring is necessary to identify signs of intolerance, hemodynamic instability and metabolic disorders. EN with intragastric location can be safely provided even for patients positioned in pronation and oxygenation by extracorporeal membrane[46].

Sepsis is associated with an initial state of systemic and hypermetabolic inflammation, with subsequent worsening of immunosuppression characterized by apoptosis and lymphocyte depletion. This later phase is also characterised by reduced capacity of monocytes and macrophages to release pro-inflammatory cytokines, further facilitating infection[50]. SARS-CoV-2 patients who develop sepsis, with or without liver complications, can benefit from early EN in combination with supplementary PN as ideal strategy to reach at least 80% of calorie needs by the third day of hospitalization. It is also recommended that protein be administered initially at low dosage (0.8 g/kg per day), progressively increased until reaching 1.3 g/kg per day after control and resolution of sepsis[48].

The transition to PN should not be delayed when it is not possible to reach energy and protein targets through the gastrointestinal tract or where contraindications for EN exist. Such patients may present intolerance to EN, characterized by classical clinical manifestations such as nausea, vomiting and abdominal distention, which evidences the need for concomitant PN administration. Another factor that may limit EN in critically ill SARS-CoV-2 patients is the placement of the post-pyloric tube, which would involve an additional aerosol generation procedure. In addition, the use of non-invasive positive pressure ventilation can prevent the use of feeding tube due to the difficulty of establishing an efficient seal with a comfortable fit[46,51].

The indication of PN for SARS-CoV-2 patients is common in intensive care, which must follow the principles and recommendations for NT in critically ill patients[46, 51]. However, frequently in SARS-CoV-2 patients there is a need to maintain PN for extended periods, which unfortunately increases the risk of metabolic disturbances and liver disease associated with intravenous (IV) infusion of nutrients. Thus, the development of hyperglycaemia, hyperlipidaemia and fatty liver disease must be considered when PN as exclusive route is used for extended period[48].

The reduction in luminal content and the absence of trophic stimuli from the intestine to the liver induced by PN may contribute to PN-associated liver disease (PNALD), or liver disease associated with intestinal failure[52]. PNALD, in addition to hyperglycaemia, steatosis and dyslipidaemia, can also induce liver fibrosis or cirrhosis if PN exclusive use is prolonged, especially without concomitant EN[53]. Although there is variability, PN-associated cholestasis can induce elevations in transaminases, AP, gamma-GT and conjugated bilirubin, which is similar to other cholestatic diseases and therefore should be investigated for their differential diagnosis. Considering the adverse effects associated with prolonged PN, EN may be relevant in preventing liver

disease as to preserve the integrity of the intestinal mucosa and maintenance of the liver gut axis[52].

Several mechanisms can explain hepatic changes induced by PN, including deterioration of the intestinal mucosa, facilitated bacterial translocation through the intestinal epithelium, inflammation, and hepatic endotoxicity. It is believed that the lack of activation of enterocyte receptors by luminal agonists, attributed to the absence of enteral feeding, may decrease signalling to the liver *via* portal circulation, interrupting the gut liver axis cross-communication[52]. The reduced blood flow to the small intestine and portal vein that occurs in PN is associated with lowered liver mononuclear cell counts, potentially contributing to hepatocellular dysfunction[54].

Hepatobiliary receptors, including the farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5, appear to have an important role on PNALD pathogenesis. Reduced activity of the human orthologous fibroblast growth factor-19 (FGF19), which exerts hepatoprotective action, as well as decreased activity of the intestinal trophic factor glucagon-like peptide-2, may be associated with PN. FXR signalling is a pathway that regulates the secretion of FGF19, a protein that modulates cholesterol 7 alpha-hydroxylase 1, which in turn limits the synthesis of bile acids. PN has been shown to inhibit this signalling pathway, inducing changes in bile acid metabolism, hepatocyte apoptosis, hepatocellular injury and liver fibrosis[53].

Hyperglycaemia is commonly observed in EN and PN and has been associated with increased risk of clinical complications and mortality during hospitalization[55]. To date, there are no specific guidelines that recommend glycaemic targets and effective strategies for the management of EN or PN-associated hyperglycaemia in SARS-CoV-2 patients. However, it is known that the elevation of inflammatory markers such as IL-6, CRP, ferritin and D-dimer are more persistent in hyperglycaemic patients during hospitalization for SARS-CoV-2. In addition, patients with hyperglycaemia or diagnosed with diabetes are at higher risk for the progression of SARS-CoV-2 disease severity when compared with normoglycaemic and those without a diagnosis of diabetes[56,57]. Glycaemic control in SARS-CoV-2 patients must include optimization of the carbohydrate content and continuous IV insulin to offer the best possible glycaemic control[56].

The source of lipids in PN is often derived from soybean oil, a source of ω-6 polyunsaturated fatty acids (PUFAs). Arachidonic acid is bioconverted to prostaglandins, thromboxanes and leukotrienes of series 2 and 4, which are pro-inflammatory and may contribute to the increased incidence of cholestasis, steatosis, sepsis, changes in neutrophil function and positive regulation of matrix metalloproteinases (MMPs)[58]. Preservation of the matrix is essential for reducing the progression of liver disease, and it is known that increased MMP activity can cause damage to the liver parenchyma [59]. It is therefore recommended that the PN prescription in SARS-CoV-2 should prioritize lipid emulsions enriched with fish oil, with doses of approximately 0.1 g/kg per day to 0.2 g/kg per day[60].

SARS-CoV-2 patients with history of liver disease require attention to the provision of NT as they may present impaired digestion and absorption of nutrients, altered protein metabolism, insulin resistance and previous nutritional deficiency. Such manifestations can negatively influence tolerance to NT, posing an additional obstacle for the daily nutritional requirements[61,62]. Table 1 presents the summary of the main general guidelines for NT for patients with liver disease or liver disorders developed in the clinical course of SARS-CoV-2 severe infection.

NUTRITION AND IMMUNE RESPONSE IN SARS-COV-2

The link nutrition — immune response is very well established: malnutrition is a risk factor for respiratory infection[63]. Previous scientific evidence shows that vitamins A, C, D, E, pyridoxine (B6), cyanocobalamin (B12), and folic acid, trace elements including zinc, iron, selenium, magnesium and copper, as well as the functionally essential ω-3 PUFAs eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, all have a paramount effect on immune function[64-67]. Evidence shows that the regular intake of functional foods containing anti-inflammatory and immunomodulatory nutrients and bioactive agents are associated with optimum immune function[12,42,68].

Nutritional recommendations for SARS-CoV-2 therapies specifically are not yet available. However, as the SARS-CoV-2 virus shares some functional similarities with other coronaviruses identified before the current pandemic, it may be expected that the scientific evidence gathered previously may be relevant for COVID-19. A summary

Table 1 Nutritional recommendations for patients suffering with chronic hepatic disease[44,45,95]

Nutrients	ESPEN 2019	ESPEN 2020		Critical care medicine 2020
		Non-obese	Obese	
Calories	30 kcal/kg per day to 35 kcal/kg per day	30 kcal/kg per day to 35 kcal/kg per day	25 kcal/kg per day	30 kcal/kg per day to 35 kcal/kg per day; Glycaemic target at 110 mg/dL to 180 mg/dL
Protein	1.2 g/kg per day to 1.5 g/kg per day	1.2 g/kg per day to 1.5 g/kg per day	2.0 g/kg per day to 2.5 g/kg per day	1.5 g/kg per day to 2.0 g/kg per day
EN + BCAA	0.20 g/kg to 0.25 g/kg	Not routinely recommended		0.2 g/kg to 0.25 g/kg

BCAA: Branched chain amino acids; EN: Enteral nutrition.

of the main scientific evidence available is presented in Table 2.

Vitamins

A recent narrative review encompassing 204 studies summarised the beneficial effects of vitamins A and E against COVID-19, mainly through their antioxidant and immunomodulatory effects, as well as activation of innate immunity and local paracrine signalling[69]. Furthermore, the beneficial effects of thiamine, vitamin C and vitamin D in respiratory diseases similar to SARS-CoV-2 and sepsis have also been identified[69]. Despite the current lack of clinical trials investigating the effects of vitamin supplementation on SARS-CoV-2, when considering pathophysiological pathways related to viral replication and the immune system, the scientific evidence available to date encourages the recommendation for said nutrients in supplemental form in the event of nutrient deficiency.

Vitamin A and its plant-derived precursor beta-carotene are often referred to as "anti-infective agents". Studies have shown a higher risk of measles and worsened outcomes in vitamin A deficiency. Vitamin A supplementation is believed to have reduced morbidity and mortality from measles, diarrhoea, pneumonia, HIV and malaria[70]. Vitamin A is known to possess antiviral properties in measles, reducing viral replication possibly due to its role in innate immunity[71]. Regarding coronavirus specifically, one study identified reduced effectiveness of coronavirus vaccine in cattle when in conditions of vitamin A deficiency[72].

Regarding the B group of vitamins, studies have shown that the combination of vitamin B2 (riboflavin) and ultraviolet radiation was able to reduce the viral load of MERS-CoV in human plasma products[73]. Vitamin B3 (nicotinamide) has shown bactericidal properties against *Staphylococcus aureus*[74]. Nicotinamide has been associated with reduced inflammation in mechanical ventilation-associated pneumonia, mainly attributed to reduction in neutrophilic migration, although hypoxemia was a negative outcome identified[75].

A recent study using *in silico* technology simulated the binding of the main protease (Mpro) of the coronavirus with a range of molecules that could potentially possess antiviral and or therapeutic effects against SARS-CoV-2[76]. The results showed that the chemical structure of cyanocobalamin (B12) and nicotinamide presented some interaction with the Mpro active site. Cyanocobalamin and nicotinamide were ranked in the 4th and 6th position, respectively, in the list of molecules tested, placed after the antivirals ribavirin and telbivudine. The authors suggest that the combined use of ribavirin, telbivudine, cyanocobalamin and nicotinamide could be tested as a potential treatment for SARS-CoV-2. A study that investigated the effects of cyanocobalamin in hepatitis C patients showed a sustained virological response (SVR) when this vitamin was added to standard antiviral therapy, suggesting that cyanocobalamin supplementation may be an independent factor associated with SVR in difficult-to-treat genotype (genotype 1) hepatitis C and in those with a higher baseline viral load[77].

Ascorbic acid has been studied widely, and previous research has reported beneficial effects in the prevention and treatment of coronavirus infections[78]. Ascorbic acid has also been associated with antihistamine effects, which alleviate some cold symptoms[79]. A clinical study carried out with 19357 individuals without pre-existing lung diseases investigated the association between plasma vitamin C levels and the risk of respiratory diseases after a three-year follow-up. The results showed that higher vitamin C plasma levels, which is an indicator of greater consumption of fruit and vegetables, were related to lower risk for chronic respiratory diseases, including pneumonia. The authors suggest that a daily intake of 3 to 5 servings of fruit

Table 2 Vitamins, nutraceuticals and bioactive compounds in supporting therapies for coronaviruses, including severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, bovine and avian coronavirus[107]

Nutrients and bioactive compounds (RDA, when available)	Effects in humans[1]	Dose	Antiviral action	Ref.
Vitamin A, [2]RDA: 700-900 μg/d, UL: 3000 μg/d or 10.000 IU	Yes (Measles, Ebola)	Until 3000 IU μg/d (children from 6 mo to 11 mo) and 60000 μg/d children 1-5 yr; Adults: 60000 μg in 2 consecutive days	Measles, Ebola, Bovine coronavirus	Mayo-Wilson *et al*[96], 2011; Aluisio *et al*[97], 2019; Jee *et al*[72], 2013
Vitamin B_2, [2]RDA: 1.1-1.3 mg/d, UL: ND (not determined)	No	2-3 times RDA[3]	MERS-CoV + UV radiation (antiseptic)	Keil *et al*[73], 2016
Vitamin B_{12}, [2]RDA: 2,4 μg/d, UL: ND	Yes	5000 μg IM (intramuscular) monthly	SARS-CoV-2 (molecular modelling), HCV	Kandeel *et al*[76], 2020; Rocco *et al*[77], 2013
Vitamin C, [2]RDA: 75-90 mg/d, UL: 2000 mg/d	Yes (ICU, pneumonia)	1-3 g/d; Inpatient: 50 mg/kg IV (intravenous) 6/6 h for 4 d; Elderly: 200 mg/d-2 g/d	Pneumonia, MERS-CoV	Hemilä[78], 2003; Field *et al*[79], 2002; Myint *et al*[80], 2019; International Society for Immunonutrition[98]
Vitamin D, [2]RDA: 5-15 μg/d, UL: 50 μg/d or 2000 UI	Yes (pneumonia, acute upper respiratory infection)	30 μg/d; Or Bolus: 2500-5000 μg/mo; Elderly: 10-100μg/d	Pneumonia, UAI, bovine coronavirus	Martineau *et al*[65], 2017; Jayawardena *et al*[67], 2020; Grant *et al*[81], 2020; International Society for Immunonutrition[98]
Vitamin E, [2]RDA: 15 mg/d, UL: 1000 mg/d or 1490 UI	No	300 mg 2xd for 3 mo or 365 mg/d for 6 mo; Elderly: (134- 800 mg/d)	Bovine coronavirus, Coxsackie	Andreone *et al*[99], 2001; Look *et al*[100], 1999; Nonnecke *et al*[83], 2014; International Society for Immunonutrition[98]
Zinc, [2]RDA: 8-11 mg/d, UL: 40 mg/d	Yes (measles, SARS-CoV)	75-100 mg/d; Elderly: 30-220 mg/d	Measles, SARS-CoV	Awotiwon *et al*[92], 2017; te Velthuis *et al*[91], 2010; International Society for Immunonutrition[98]
Selenium, [2]RDA: 55 μg/d, UL: 400 μg/d	Yes (influenza)	200 μg/d	Influenza, Avian coronavirus	Hoffmann and Berry[86], 2008; Ma *et al*[85], 2019
Omega-3	Yes (influenza)	1-3 g/d[3]	Influenza, HCV	Cai *et al*[66], 2018
Quercetin	No	1 g/d	SARS-Cov (*in vitro*), IVAS	Chen *et al*[101], 2006; Heinz *et al*[102], 2010
Green tea/catechins (EGCG)	No	4 cups/d or 225 mg de EGCG[4]	Bovine coronavirus (*in vitro*)	Clark *et al*[103], 1998
Resveratrol	No	100-150 mg 2 × d[3]	MERS-CoV (*in vitro*)	Lin *et al*[104], 2017
Curcumin	No	0.5-1 g/d[3]	SARS-CoV(*in vitro*)	Wen *et al*[105], 2007
Lipoic acid	No	600 mg/d[3]	Human coronavirus 229E (*in vitro*)	Wu *et al*[106], 2008

[1]We did not find any work related to this substance and anti-viral or anti-infectious action in humans.
[2]For adult patients, according to age group and gender.
[3]Usual dose employed in clinical practice.
[4]Epigallocatechin.
RDA: Recommended dietary allowance; UAI: Upper airway infection; UL: Tolerable upper intake levels; ICU: Intensive care unit.

and vegetables may provide adequate intake of vitamin C and promote significant health benefits for the general population[80].

Vitamin D, with its important hormonal actions, acts on several components of the immune system, including the synthesis of cathelicidin, an endogenous antimicrobial peptide. A meta-analysis covering over 11000 individuals showed that vitamin D supplementation, even when its serum levels are adequate, can reduce by 25% (adjusted OR: 0.75; 95%CI: 0.60-0.95) the chance of contracting infections of the upper and lower airways, with a more expressive result (70% of cases) for those with baseline levels of 25-hydroxyvitamin D (25(OH)D) below 25 nmol/L (adjusted OR: 0.30; 95%CI: 0.17-0.53)[65]. A systematic review of 42 clinical studies testing the effects of vitamins, minerals, nutraceuticals and probiotics on immunological markers of patients with

viral and respiratory infections showed that vitamins A and D were associated with better outcomes, an effect that was more predominant in populations deficient in those nutrients[67].

A recent narrative review discussed the relationship between vitamin D deficiency and the risk for influenza and COVID-19, and further emphasized the increased risk in aged individuals and in those suffering with chronic comorbidities[81]. Their recommendations to reduce the risk of influenza and COVID-19 infections involve 10,000 IU vitamin D3 supplementation daily for a few weeks to rapidly increase 25(OH)D serum levels. This period would be followed by a maintenance daily dose of 5000 IU to maintain 25(OH)D above 40 ng/mL to 60 ng/mL (equivalent to 100 nmol/L to 150 nmol/L). However, randomized clinical trials and large population studies must be conducted to evaluate the effectiveness of such recommendations.

Vitamin E, including α-tocopherol and tocotrienol, is a potent fat-soluble antioxidant found in significant concentration in immune cells. Some evidence suggests that the currently recommended vitamin E intake may be low, and that its supplementation above current dietary recommendations favoured immune function and reduced the risk of infection, especially in the elderly. Vitamin E contributes to T cell membrane integrity, signal transduction and cell division, and also indirectly by attenuating inflammatory mediators released by other immune cells. The modulation of immune function by vitamin E has clinical relevance, as it affects the host's susceptibility to infectious diseases and respiratory diseases such as asthma and pneumonia [68].

Vitamin E supplementation was found to have different responses upon the incidence of pneumonia when factoring smoking and levels of physical activity[82]. Vitamin E reduced the risk of pneumonia by 69% in participants who had lower exposure to smoking and performed more physical exercise. In the opposite direction however, vitamin E supplementation increased the risk of pneumonia by 68% in the individuals who had greater exposure to smoking and did not exercise. Interestingly, a study in calves has shown greater risk of coronavirus infection in the vitamin E-deficient animals[83]. Overall, such findings suggest that the effects of vitamin E supplementation upon pneumonia risk are likely to be positive but may not be uniform and therefore caution is recommended when supplementing, balancing benefit against risk.

Trace elements

Selenium deficiency has been associated with reduced immune response and greater virulence of some benign viruses[84]. An experimental study in birds showed that selenium supplementation associated with ginseng increased the immune response against avian coronavirus[85]. Selenium deficiency was associated with mutations in genomic RNA that can potentially influence the virulence of certain RNA viruses, such as influenza A virus[86]. Clinical benefits associated with the potential immunomodulatory effects of selenium supplementation have also been demonstrated in other viral infections, including HIV-1[87]. A randomized controlled study found that selenium supplementation reduced the viral load in HIV patients[88]. Lastly, a systematic review assessing the effects of mineral supplementation upon immunological markers in patients diagnosed with respiratory infections of viral origin showed that selenium and zinc had favourable immunomodulatory effects, improving the clinical evolution in viral respiratory infections[67].

It is known that the risk of developing pneumonia associated with mechanical ventilation is high, especially when the use of respirators is prolonged, as in the most severe cases of SARS-CoV-2. A randomized clinical study carried out with 99 critically ill patients investigated the effects of selenium infusion compared to isotonic saline for 10 d. Selenium infusion increased not only its serum levels but also the concentration of glutathione peroxidase-3, but it did not reduce the incidence of pneumonia or mortality of the critically ill patients evaluated[89]. In view of the evidence presented, there is a possibility that selenium levels may influence the clinical evolution of SARS-CoV-2, but such suggestion can only be confirmed or rejected through well-designed clinical research.

Zinc is the second most abundant trace element in the body; it is present in the cytoplasm as a cation and in the blood it is associated with metalloprotein[90]. It is an important trace element for cell maturity in both the innate and acquired immune systems, in addition to having antiviral properties. It has been shown that the replication of SARS-coronavirus, hepatitis C virus and influenza virus (H1N1) can be inhibited by zinc oxide or salt[90,91]. In addition, zinc supplementation in children diagnosed with measles reduced morbidity from pneumonia associated with this infection[92]. The antiviral properties of zinc are not yet well defined, but they are

possibly related to the inhibition of viral binding to the mucosa, inflammation suppression, synthesis of antiviral interferon and inhibition of the enzyme necessary for viral replication[90,91].

Several clinical trials are currently being developed investigating the effectiveness of chloroquine as anti-coronavirus agent. It has been hypothesized that the mechanism of action of chloroquine may involve the induction of zinc uptake into the cytosol, a mechanism that could be associated with inhibition of the viral RNA polymerase inside the infected cell [90]. Future clinical trials shall explore any potentially synergistic role of zinc and chloroquine in SARS-CoV-2 patients.

Essential fatty acids

Essential fatty acid deficiency can result in late or insufficient resolution of inflammation, which can be a determining factor for the evolution of SARS-CoV-2 to the most severe forms, characterized by intense inflammation[63,93]. A meta-analysis assessing clinical studies that employed nutritional formulae containing EPA and DHA for patients with ARDS identified a significant improvement in blood oxygenation and a reduction in the need for mechanical ventilation, organ failure, ICU length of stay and mortality at 28 d of hospitalization[94]. Such results suggest an important effect of EPA and DHA in improving inflammation and lung injury, probably due to anti-inflammatory mediators including resolvins, protectins and maresines and others, which are derived from EPA and DHA[63,94].

CONCLUSION

Hyperglycaemia, a common feature of severe SARS-CoV-2 infection induced by glucocorticoid hypersecretion associated with metabolic stress, should not be neglected in SARS-CoV-2 therapies due to the additional risk of immune suppression. The unfavourable biochemical environment observed in obesity and diabetes contributes to immune dysregulation and has been described as an important determinant in SARS-CoV-2 outcomes.

COVID-associated liver injury often occurs in the evolution of SARS-CoV-2 into more severe stages and can affect patients with or without pre-existing liver disease. Furthermore, pharmacotherapies including macrolide or quinolone antibiotics and steroids can also induce liver damage. The presence and exacerbation of liver disease are directly associated with more negative outcomes in SARS-CoV-2.

NT guidelines for liver patients affected by SARS-CoV-2 in intensive care, specifically, are not yet available. For that reason, strategies for the management of conditions such as sepsis and severe acute respiratory distress syndrome are suggested. EN poses several advantages, namely lower cost, overall lower risk, preservation of splanchnic blood flow and intestinal trophism, and maintenance of enterocyte barrier. NE with intragastric location can be provided for patients positioned in pronation and oxygenation by extracorporeal membrane. An iso-osmolar standard polymeric formula designed for gradual administration with initial protein content at 0.8 g/kg per day progressively increasing up to 1.3 g/kg per day and enriched with fish oil at 0.1 g/kg per day to 0.2 g/kg per day is often recommended. Transition to PN should not be delayed when it is not possible to reach energy and protein targets through the gastrointestinal tract or where contraindications for EN exist. As prolonged PN may contribute to PNALD, EN should always be considered whenever possible. As EN or PN-associated hyperglycaemia is another factor to consider, glycaemic control in SARS-CoV-2 patients must include optimization of the carbohydrate content and continuous IV insulin to offer the best possible glycaemic control.

For patients who have not developed the more severe forms of SARS-CoV-2, the following recommendations can be made: (1) Optimal nutrient intake can help reduce the impact of SARS-CoV-2 and possibly limit the evolution to more severe forms; (2) Early health interventions in obesity, type 2 diabetes, heart, lung and liver disease are effective preventative strategies against SARS-CoV-2; (3) Supplementation with the micronutrients and omega-3 fatty acids described in the present study is a safe, effective and low-cost strategy to help stimulate optimal immune function; (4) Supplementation beyond the Recommended Dietary Allowance can be considered, but only within the upper safe limits (maximum tolerable intake — tolerable upper intake level — UL) for specific nutrients such as vitamins C and D; and (5) Public health authorities are encouraged to include nutritional strategies in their recommendations so that public health policies can assist in the efforts against respiratory diseases of

viral origin.

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