Rev Esp Nutr Hum Diet. 2021; 25 (Supl. 2): e1073
Nutrición y Dietética en COVID-19

Freely available online - OPEN ACCESS

Revista Española de Nutrición Humana y Dietética
Spanish Journal of Human Nutrition and Dietetics

REVIEW ARTICLE

Nutritional Therapy in Critically Ill Patients with COVID-19: A Narrative Review

Terapia Nutricional en Pacientes Críticamente Enfermos con COVID-19: Revisión Narrativa

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Received: 26/05/2020; Accepted: 29/07/2020; Published: 11/09/2020

CITA: Guilherme LG. Nutritional Therapy in Critical Ill Patients with COVID-19: A Narrative Review. Rev Esp Nutr Hum Diet. 2021; 25 (Supl. 2): e1073. doi: 10.14306/renhyd.25.S2.1073

ABSTRACT

Introduction: Combating the pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), better known as Coronavirus Disease 2019 (COVID-19), in all countries of the world has been a challenge. Most patients can be treated in home isolation, however elderly patients and/or with associated comorbidities have been demonstrating more severe conditions of the disease, requiring hospitalization, or even nutritional therapy and mechanical ventilation. Objective**:** To review the current evidence to establish better nutritional recommendations for critically ill patients with COVID-19.

Material and methods: This is a narrative review on nutritional therapy in critical patient with COVID-19. The scientific articles were searched in the databases U.S. National Library of Medicine (PubMed), as well as their respective terms in Portuguese and Spanish, and 40 articles were chosen, excluding the guidelines that were used to help better compose this article.

Results: The main findings were that age and non-communicable diseases are considered risk factors for mortality, with systemic arterial hypertension and diabetes mellitus being the main ones. These patients need special care, as well as constant assessment of nutritional status, since malnourished and obese patients have shown a high association with mortality and the use of mechanical ventilation. Nutritional therapy in the affected patients can improve clinical outcome and should be considered as first-line treatment and be more valued in the hospital setting. Although there is no recommendation for supplementation of vitamin C and D and the mineral zinc, these may bring benefits to the immune system of these patients and help in a better prognosis of COVID-19, however more studies are still needed to substantiate the dosage.

Conclusions: Further studies are needed, but it is important to bring these themes already exposed by some authors to stimulate discussions that might lead to improvements in the standardization of nutritional approaches.

Keywords: Nutrition Therapy; Nutritional Status; *COVID-19*; *SARS-CoV-2*.

RESUMEN

Introducción: La lucha contra la pandemia causada por el Síndrome Respiratorio Agudo Severo Coronavirus 2 (SARS-CoV-2), más conocido como Enfermedad por Coronavirus 2019 (COVID-19), en todos los países del mundo ha sido un desafío. La mayoría de los pacientes pueden ser tratados en aislamiento domiciliario, sin embargo, los pacientes de edad avanzada y/o con comorbilidades asociadas han demostrado condiciones más severas de la enfermedad, que requieren hospitalización, o incluso terapia nutricional y ventilación mecánica. Objetivo: Revisar la evidencia actual para establecer mejores recomendaciones nutricionales para pacientes críticamente enfermos con COVID-19.

Material y métodos: Esta es una revisión narrativa sobre la terapia nutricional en pacientes críticos con COVID-19. Los artículos científicos fueron buscados en las bases de datos U.S. National Library of Medicine (PubMed), así como sus respectivos términos en portugués y inglés, y se eligieron 40 artículos, excluyendo las pautas que se utilizaron para ayudar a redactar mejor este artículo.

Resultados: Los principales hallazgos fueron: La edad y las enfermedades no transmisibles se consideran factores de riesgo de mortalidad, siendo las principales hipertensión arterial sistémica y diabetes mellitus. Estos pacientes necesitan cuidados especiales, así como una evaluación constante del estado nutricional, ya que los pacientes desnutridos y com obesidad han mostrado una alta asociación con la mortalidad y el uso de ventilación mecánica. La terapia nutricional en los pacientes afectados puede mejorar el resultado clínico y debe considerarse como un tratamiento de primera línea y ser más valorado en el entorno hospitalario. Aunque no hay ninguna recomendación para la suplementación de la vitamina C y D y del zinc mineral, éstos pueden traer ventajas al sistema inmune de estos pacientes y ayudar en un mejor pronóstico de COVID-19. Sin embargo, son necesarios más estúdios para corroborar la correcta dosificación.

Conclusiones: Se necesitan más estudios, pero es importante llevar estos temas ya expuestos por algunos autores para estimular discusiones que puedan conducir a mejoras en la estandarización de los enfoques nutricionales.

Palabras clave: Terapia nutricional; Estado nutricional; *COVID-19; SARS-CoV-2.*

KEY MESSAGES

- The nutritional status of these patients has a high association with mortality and the use of mechanical ventilation, so the evaluation of the nutritional status should be considered a basic vital sign.
- Diabetic and hypertensive patients need special attention and care since it is believed that both diseases are associated with increased severity of symptoms and complications of SARS-CoV-2.
- Nutritional therapy in COVID-19 patients can improve clinical outcomes and should be considered as the first-line of defense treatment and be more valued in the hospital setting.
- Although there is no recommendation for supplementation of vitamin C and D and the mineral zinc, as they may bring benefits to the immune system of these patients and help in a better prognosis of COVID-19, although more studies are still needed to substantiate the dosage.

INTRODUCTION

Combating the pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in all countries of the world has been a challenge, as it threatens the health of the population and the overwhelming of the health system. It is a pathology that mainly affects the respiratory system although it also can lead to multiple organ failure and even be fatal in some cases[1,2], being so far responsible for more than 590,000 deaths worldwide[3]. Most patients can be treated in home isolation, but elderly patients and/or with associated comorbidities have been demonstrating more severe conditions of the disease, requiring hospitalization, or even nutritional therapy (NT) and mechanical ventilation (MV)[1,2].

The percentage of admission to the intensive care unit (ICU) varies between countries, states, and provinces, which may be due to the availability of beds in the ICU, as well as the criteria used for admission may be different. An example is the study by Huang et al. (2020) where out of 23 severe patients only 11 were admitted to ICU[4], and another study in the same country, but in different provinces showed a much higher number of admissions to intensive care[5].

During the acute phase of this infection, it is common for patients to experience hypermetabolism that will lead to exacerbation of lean mass depletion and an energy deficit, and associated with the critical disease will advance to a worse prognosis, as well as affect the nutritional status of these individuals[6,7]. These patients may still have difficulty feeding orally, either due to the symptomatology of the disease or due to the use of MV so, the timing of nutritional intervention should be critically and carefully analysed[2,6,7].

Beds in ICU have been increasingly full and even exceed their maximum capacity in many places due to respiratory failure caused by more severe forms of the disease[8]. Therefore, at this time, it is important to prevent the transmission of the virus to reduce the number of new infected persons so that hospitalized patients can have better care and treatment while in hospitals.

As it is a novel disease, there are no specific nutritional recommendations for these patients as yet, there are some suggestions based on clinical experience with SARS-CoV-2, critical patients, and other previously known severe respiratory diseases. Therefore, the objective of this review was to describe the clinical and nutritional characteristics of critical patients diagnosed with Coronavirus Disease 2019 (COVID-19) to help establish better nutritional recommendations for these and future patients.

MATERIAL AND METHODS.

Narrative review of scientific articles conducted for the analysis of available content on nutritional therapy in critical patients with COVID 19, demographic, clinical and nutritional characteristics of this group.

Search strategy.

The search for the scientific articles that were part of this work was carried out between April and July 2020 in the database U.S. National Library of Medicine (PubMed). In the search field was placed "COVID-19 or Coronavirus OR SARS-CoV-2" added the following terms, separately: "Critical patient", "ICU", "nutritional therapy" and "nutritional status" as well as their respective terms in Portuguese and Spanish. The data used were analyzed in conjunction with the existing recommendations published by the American Society for Parenteral and Enteral Nutrition (ASPEN), Brazilian Society of Enteral and Parenteral Nutrition (BRASPEN) and European Society for Parenteral and Enteral Nutrition (ESPEN).

Eligibility Criteria.

The eligibility criteria of the studies so that they could be considered for review were that these were articles published between the years 2019 and 2020 in Portuguese, English, or Spanish. It was also part of the criteria that the full text of the study was available for reading online or for download. Conference summaries were excluded, as well as s redundant or not pertinent articles. Articles made with children, adolescents and pregnant women were also excluded.

Selection of Studies and Data Extraction.

The types of studies included in the formation of this narrative review:

1. Observational studies: the majority were of the case series type, despite the limitation of this type of study (non-randomized sample, lack of a control group, observations of atypical situations), it is ideal to describe subjects not yet well known and are important sources of hypotheses. A cross-sectional study was also used, ideal for measuring prevalence. And finally, a retrospective cohort study, which is useful for diseases with long latency period, which is the case of COVID-19.

2. Reviews: most of the systematic type, with or without meta-analysis, which are at the top of the pyramid of scientific evidence, because they are methodical, minimize biases and ensure quality. The systematic review with meta-analysis were used to reinforce the findings of observational studies since clinical trials are still scarce in the literature. Some narrative reviews

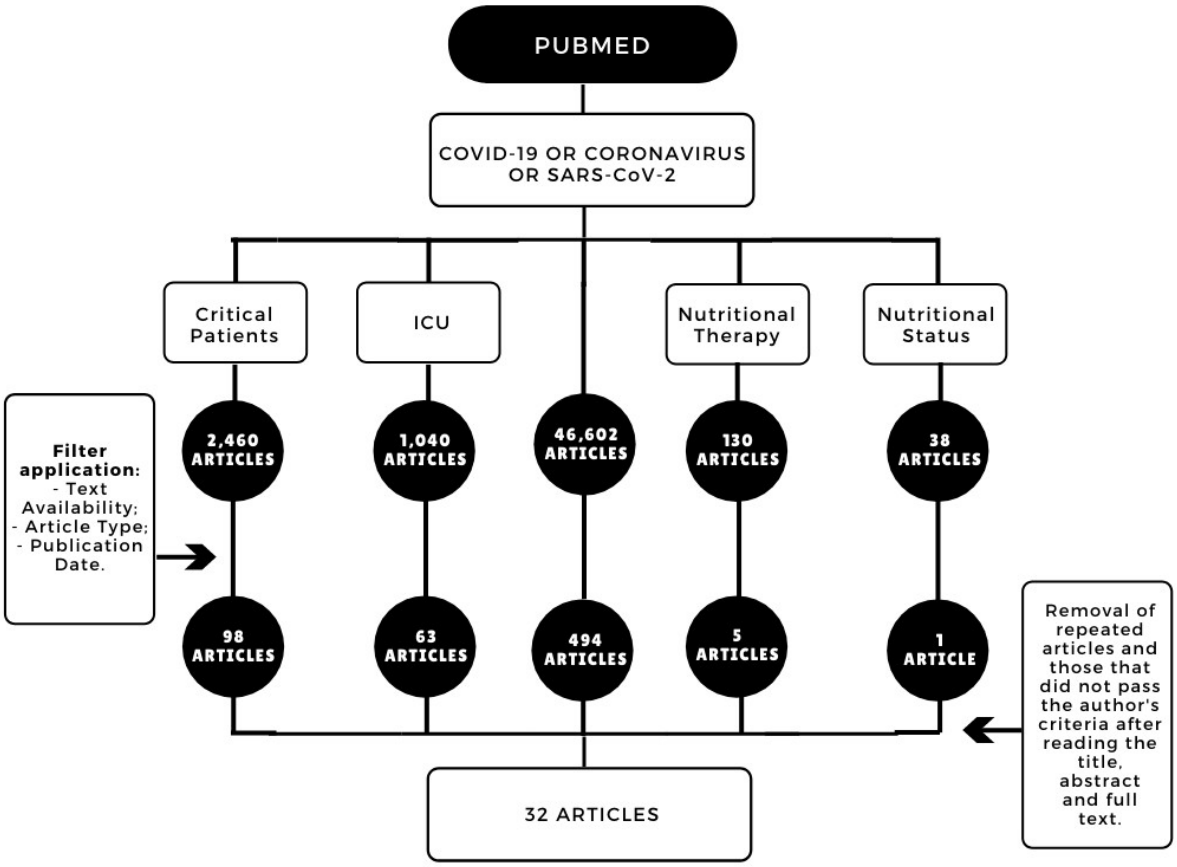
were used to compose the topic about micronutrients and hydration, and although they make a predominantly qualitative synthesis, they have broader questions.

3. Randomized Controlled Trials: These were selected to help in a better understanding of the dosage of vitamins C and D in these patients.

4. Guidelines.

The initial search in the database resulted in several studies on the subject, after the first stage where the filters were applied: text availability (full text), date of publication (1 year) and type of articles (Clinical Trials, Guidelines, Meta-Analysis, Systematic Review, Observational and Multicenter Study). Thus, the articles that did not meet these criteria were excluded, remaining 494 articles on the topic in general , 98 articles related to the term "critical patients", 63 articles to the term "ICU", 5 articles to the term "nutritional therapy" and only 1 for "nutritional status". The next step was the elimination of the articles that appeared repeatedly and with the remaining articles was started a selection through the analysis of titles, abstracts and if the content was associated with the purpose of the review, these were followed to the full reading process of the article to ensure its relevance. After reading, 32 articles were chosen for this review, as shown in the flowchart (Figure 1), but 4 additional studies were located through review of the reference lists of the above articles.

Figure 1. Flow Chart of study selection process.



The second research was for the topic "hydration" and “micronutrients” due to scarcity in the literature, an exception was opened for the inclusion of literature reviews to better discuss these topics. In the search field was placed "COVID-19 or Coronavirus or SARS-CoV-2" added to the term " hydration", 112 articles were founded, but when adding the filters, 15 articles remained. These articles underwent the same type of analysis as the previous ones, and 2 were chosen for this review. The same thing was done with the term "micronutrients" where first was found 126 articles, after application of the filter remained 18 articles and after analysis of the author, 2 articles were chosen. 2 randomized clinical trials have been added to assist in the composition of this topic for a better understanding of dosages and effects.

All data were placed in sheets mounted in Microsoft Excel, where they could be better analyzed, and averages were calculated.

RESULTS

Demographic and clinical characteristics

The percentage of admission to the ICU varies between countries, countries, states, and provinces where a range of 5.4%-26.1% was found[4,5]. Grasselli et al. (2020), in Italy, revealed that 9% of the patients who presented more severe conditions of the disease required ICU[9]. On the other hand, a study in the USA found higher values, where 22% of these patients required intensive care[10] (Table 1).

Table 1. Demographic and clinical characteristics of the patients in the studies considered.

Author	Country	No patients	Average age	Men %	ICU Admission	NCDs %	DM %	SAH %	CVD %	CRD %	RS %	Mortality %
Huang et al.[4]	China	202	49.0	73.9	5.4	39.1	34.8	8.7	34.8	4.30	100.0	0.0
Wang et al.[5]	China	138	66.0	61.1	26.1	72.2	22.2	58.3	22.2	8.30	100.0	16.7
Pedersen et al.[8]	Denmark	16	69.5	75.0	--	81.3	13.0	56.0	13.0	19.00	100.0	43.8
Grasselli et al.[9]	Italy	1,591	63.0	82.0	9.0	68.0	17.0	49.0	17.0	4.00	99.0	26.0
Cummings et al.[10]	USA	257	62.0	67.0	22.0	82.0	36.0	63.0	36.0	17.00	100.0	39.0
Shahriarirad et al.[11]	Iran	113	53.8	63.6	9.7	38.9	27.3	45.5	27.3	18.20	81.8	45.5
Simonnet et al.[12]	France	124	60.0	73.0	--	98.4	23.0	49.0	23.0	--	100.0	15.0
Yang et al.[13]	China	52	59.7	67.0	7.70	40.0	17.0	--	17.0	8.00	100.0	61.5
Yu et al.[14]	China	226	64.0	61.5	--	68.6	20.8	42.5	20.8	6.60	95.1	4.0
Average	**--**	**--**	**60.77**	**75.71**	**11.12**	**67.16**	**21.38**	**47.12**	**21.38**	**6.56**	**98.25**	**24.1**

NCDs: Non-Communicable Diseases. DM: Diabetes Mellitus. SAH: Systematic Arterial Hypertension. CVD: Cardiovascular Disease.

The main reasons for admission to the ICU were acute hypoxemic respiratory failure and development of multiple organ dysfunction[4,5,8-13]. People of different age groups are susceptible to infection with SARS CoV-2, but it was noticed that the elderly are the ones who occupy the most ICU beds, because they develop more severe forms of COVID-19. Koh et al. (2020) expressed that elderly patients were perhaps more prevalent due to their weak innate immunity accompanied by an over-reactive adaptive immune system induced by the virus, which leads to inflammatory responses causing complications such as acute respiratory distress syndrome (ARDS) the biggest factor of ICU admission[15]. Grasselli et al. reported that advanced age alone does not represent a risk factor for ICU admission[9] so, it is possible that the high age found in this population may also be due to the high prevalence of non-communicable diseases (NCDs) among the elderly[2,16]. It was also detected that more than 50% of these patients are male[4,5,8-14]. It is suggested that female sex hormones and protection of the X chromosome are involved in innate and adaptive immunity and therefore the number of hospitalized women is lower[11].

In relation to associated comorbidities, an American study showed that 82% of patients requiring intensive care had at least one chronic disease, with systemic arterial hypertension (SAH) being the most prominent (63%)[10]. Research conducted in Wuhan, China, revealed that 72.2% of patients had at least one associated comorbidity, where more than half were hypertensive[5]. While in Iran, it was reported that 38.9% had associated comorbidities, probably due to the difference in diet[11].

After analysis of 12 meta-analysis in COVID-19 and NCDs, all of them reported that SAH was associated with worsening of the disease[15-26] (Table 2). And 9 reported that Diabetes Mellitus (DM) was also related[15-17, 21-26]. The three articles that did not report DM were focused on SAH which leads to believe the strong correlation of both NCDs with the severity of COVID-19.

Table 2. Meta-analysis with COVID-19 and NCDs.

Author	No. Studies	No. Patients	DM %	SHA %	CVD %	CRD %
Koh et al.[15]	10	578	10	17**	12**	**
Yang et al.[16]	7	576	9.7	21.1**	8.4**	1.5**
Li et al. [17] *	6	1527	11.7[1]**	28.8[1]**	16.7[1]**	-
Zhang et al.[18]*	18	4505	-	37.58[1]	-	-
Lippi et al. [19] *	13	2893	-	34.25[1]	-	-
Pranata et al. [20] *	30	6560	-	**	-	-
Rodriguez-Morales et al.[21]	19	2874	11.9	18.6	14.4	-
Wang et al.[22]	6	1558	**	**	**	**
Espinosa et al.[23]	42	1661[1]	17[1]	26[1]	18[1]	7[1]
Hu et al.[24]	21	47344	44.5[1]**	41.7[1]**	4.7	
Potere et al.[25]	44	14866	10.7	23.3**	9.4	2.8
Tahvildari et al.[26]	80	417	11	19	8	12

*: Studies focused on SAH. **: Did not give values but showed risk of severity/exacerbation of the disease. 1: ICU values. DM: Diabetes Mellitus. SAH: Systemic Arterial Hypertension. CVD: Cardiovascular Disease. CRD: Chronic Respiratory Disease.

In meta-analysis by Li et al. (2020) the proportion of SAH and cardio-cerebrovascular disease were both statistically significantly higher in critical patients when compared to non-critical patients, and also reported that cardiovascular diseases (CVD) and DM increase the risk of mortality twice[17]. It is worth noting that it is not that patients with comorbidities such as SAH, DM and cardio-cerebrovascular disease are more susceptible to infection with SARS-CoV-2, but rather that they are more likely to develop more severe forms of the disease[17].

Zhang et al. (2020) showed that patients with SAH had 2.27-fold higher risks of severity compared to those without SAH, and that the presence of this comorbidity could independently increase the risk of disease severity and predict worse clinical outcomes[18]. Another meta-analysis showed similar value, where hypertensive patients presented 2.5-fold higher risk of severe COVID-19[19]. It is not yet known the exact mechanism that leads to greater severity and mortality among hypertensive patients, but it is believed to be related to the theory that SARS-CoV-2 binds to its target through the angiotensin-converting enzyme 2 (ACE2) which is responsible for enhancing anti-inflammatory and antioxidant roles and is considered a protective factor against increased blood pressure. Therefore, it is rational to hypothesize that SARS-COV- 2 may reduce the physiological function of ACE2, leading to the reduction of angiotensin-II degradation, increased aldosterone secretion, and consequently the loss of potassium through urine, providing a potential mechanism for the severity of symptoms, multiple organ dysfunction and ARDS that can be seen with severe infection SARS-CoV-2[11,15,17-20].

A multicenter retrospective study conducted by Huang et al. (2020) disclosed that DM2 was independent risk factor of severe illness in patients with COVID-19[4]. Yan et al. (2020) noted that a more severe inflammatory response is detected in diabetic patients, just as they were more conducive to ICU admission, receiving MV, longer hospital stay and higher mortality rates, where 81.3% of diabetics died, in addition to having the lowest albumin levels[27]. Grasselli et al. (2020) found that diabetic patients were more likely to receive MV[9]. Another study reaffirmed the higher risk of diabetic patients being admitted to intensive care, the need for MV and higher mortality rates, due to glycemic variability found among them, and the high blood glucose levels have been reported as possible disruptors of the defensive capacity of the airway epithelia, secondary to the increase in its concentration in epithelial secretion[28].

Hyperglycemia is a risk factor for mortality also due to exacerbation of the inflammatory response and inflammatory indicators, especially tumor necrosis factor (TNF-alpha) and interleukins (IL)[27]. Pedersen et al. (2020) assume that the respiratory failure found in these patients is related to inflammation[8]. Zhu et al. (2020) believes that DM generates a dysregulation

in the immune response and may be the probable cause of the aggravation of COVID-19 in diabetic patients, as well as by lymphopenia and increased neutrophil levels, serum CRP, and IL-6[28].

In addition, DM is associated with the activation of the renin-angiotensin system in different tissues and tend to have an increase in ACE2 expression[11,28]. As previously mentioned, SARS-CoV-2 uses ACE2 to bind and enter cells and reduces the expression of ACE2, and overactivation of the renin-angiotensin system may contribute to increased adverse risks in this population[28]. Zhu et al. (2020) also showed a significant association between blood glucose levels, SAH and ARDS, which reinforces this theory of virus and ACE2[28].

According to a study conducted in Italy with 1591 patients, about 99% required MV, where 88% needed endotracheal intubation and 11% needed non-invasive ventilation[9]. Wang et al. (2020) reported that all critical patients received some type of respiratory support[5], reinforcing the understanding that patients in intensive care with COVID 19 commonly need this respiratory aid that will consequently affect their diet and nutritional status (NS).

Regarding mortality rates, the results found were very varied, including among studies in the same country. Of the 4 studies used that were conducted in China, the mortality rate ranged from 0% to 61.5%[4,5,13,14]. Yang et al. (2020) presented that mortality was associated with age (>65 years) with comorbidities and ARDS[13]. Research conducted in the USA, showed that 41% of the patients who died were receiving MV[10]. In the United Kingdom, 32% of the patients admitted to the ICU died and 37% of those who received MV also died, these had a mean age of 61 years[29]. Systematic review analyzing mortality in critical patients with COVID-19 indicated a mortality rate of 25.7%[30]. A study focused on the mortality of these patients showed a predominance of males aged over 50 years and with NCDs. The greatest cause of mortality was due to respiratory failure (46.91%)[31].

It is important to analyze these data with caution, since the follow-up time is different between studies, and there are studies with short follow-up time relatively short compare with the course of the disease, which will result in a lower rate.

Nutritional status

It is known that SARS-CoV-2 targets ACE2 which is also expressed in the epithelial mucosa, and it is believed that for this reason it causes gastrointestinal (GI) symptoms, such as diarrhea, abdominal pain, nausea, vomiting, anorexia[32-36] which are common and consequently will impair the feeding, absorption of nutrients and the NS of these patients[2,32].

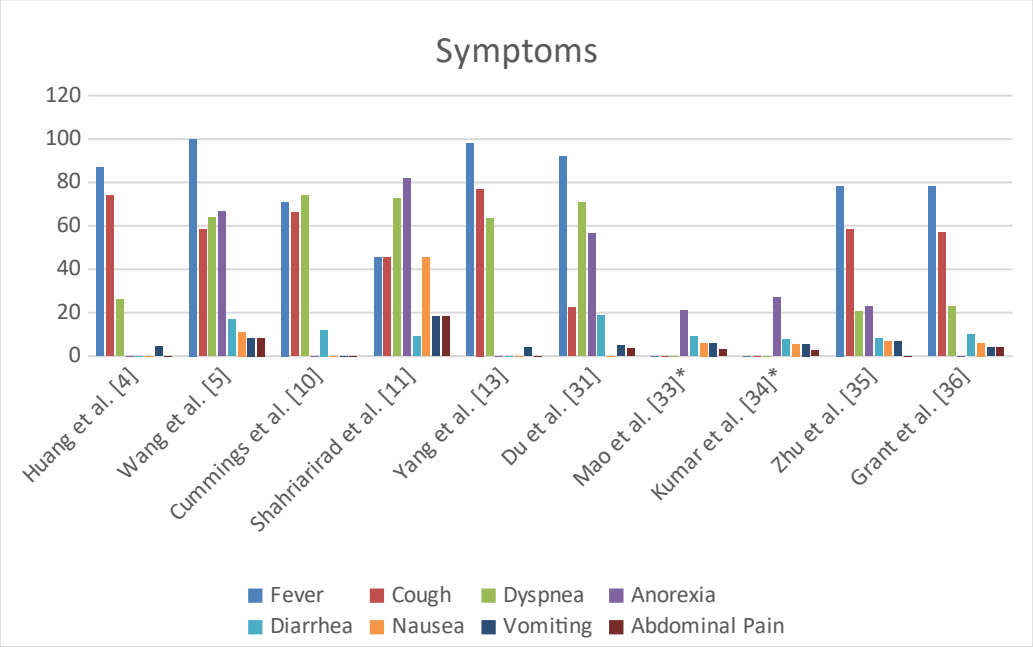
A meta-analysis by Mao et al. (2020) demonstrated that patients with GI symptoms were more frequently found in severe or critical conditions and that abdominal pain was more reported among these patients compared to non-severe, in addition, they still had a higher risk of developing ARDS and liver injury[33]. Kumar et al. (2020) reinforced the findings of Mao et al. (2020) where critical patients were over 7.17 times more likely to develop abdominal pain[34]. ASPEN (2020) reported that GI symptoms are common in critical patients so, it is difficult to know if the relationship of these symptoms are actually associated with SARS-CoV-2[6]. Abdominal pain is one of the causes of GI intolerance to diet, but since these studies did not evaluate NT, it is difficult to make this correlation[6].

The biggest problem is that GI symptoms are usually not associated with COVID-19, being considered atypical manifestations, which can be seen from the study by Mao et al. (2020) who reported that about 10% of patients presented GI symptoms alone, without respiratory characteristics and they had delayed diagnosis, but this symptomatology is being increasingly reported with the progress of the pandemic[33,35]. This time of GI symptoms and worsening of the condition without a diagnosis, favors the increased nutritional risk of these patients.

A quite common symptom is anosmia (loss of smell) and ageusia (loss of taste)[37]. Lechien et al. (2020) highlighted patients with mild to moderate forms of COVID-19, where there was a significant association between olfactory and gustatory dysfunctions, as well as fever and anosmia. Some viruses can lead to these dysfunctions due to an inflammatory reaction of the nasal mucosa, which may appear before any other more commonly reported symptoms of the disease, and may also contribute to a decrease in food intake, further favoring the worsening of EN and the need for hospitalization among these patients[37].

The most common symptoms found in COVID-19 patients is fever and cough[33-36], and diarrhea is the most common GI symptom found among these patients[33-36]. These symptoms are exposed in Figure 2.

Figure 2. Most common symptoms in the patients in the studies considered.



The presence of the virus in the GI tract, can be recognized by host immune cells, resulting in systemic cytokine release responsible for the systemic inflammatory response to the intestine, which leads to an alteration of the gut microbiota which, in turn, may cause a disturbance in the lung microbiota and increase the risk of developing ARDS[33]. This acute inflammatory response and higher concentrations of inflammatory factors were found among patients who needed ICU, suggesting that the cytokine storm was associated with the disease gravity[17], subsequently, a protein catabolism, worsening the prognosis.

Meta-analysis by Aziz et al. (2020) showed that hypoalbuminemia was associated with the severity of COVID-19 and that it could serve as a predictor of critical disease and mortality[38], but it should not be used as a marker of nutritional status, since it is a negative acute phase protein with low values in response to inflammation[7].

Malnutrition and loss of lean mass is common during ICU stay due to the effect of catabolic hormones, hypermetabolism, low food intake, and physical immobilization[7]. Elderly patients present a higher nutritional risk due to the higher prevalence of NCDs among this population, besides there are changes in body composition secondary to aging, known as sarcopenia which is defined as a loss of muscle mass and/or function that can be aggravated when associated with chewing problems[2,7]. This condition is also often found in malnourished patients admitted to the ICU[7].

A study conducted in China showed that among elderly patients infected with SAS-Cov-2, 52.7% were malnourished and 27.5% were at risk of malnutrition, they evaluated the nutritional status of elderly inpatients with COVID-19 using the Mini Nutritional Assessment (MNA). When comparing the groups not malnourished, at risk of malnutrition and malnourished, there were statistical differences in the incidence of DM, BMI, calf circumference, albumin, hemoglobin, and lymphocyte count among the three groups, where the malnourished had the lowest values[32]. Although MNA is not the most appropriate method to assess malnutrition, considering the current pandemic of COVID-19, the use of bioelectric impedance is not recommended, and even if it is a good method for detecting sarcopenia, it should be avoided, aiming at reducing the contact of the nutritionist with the patient to reduce the risk of exposure, in addition to maintaining a good inventory of personal protective equipment (PPE)[6,7].

Since it is known that age, the presence of associated comorbidities and critical disease lead to sarcopenia, it is important to reinforce the idea of an appropriate nutritional intervention. It is worth noting that malnutrition is not defined only by low body mass, but also by the inability to preserve healthy body composition and skeletal muscle mass, people with sarcopenic obesity

also apply in the criteria[2,7]. In a cross-sectional study conducted by Li et al. (2020), it was shown that patients who were not malnourished or at risk of malnutrition had higher BMI, indicating overweight (25.6 ± 3.0 kg/m2)[32].

The proportion of obese patients varies according to the countries, since eating habits are different among them. Table 3 shows studies where BMI of overweight and obesity were found, considering that not only thinness is an impasse for a better prognosis, and it is known that abdominal obesity generates an increased secretion of adipokines and cytokines, thus generating a chronic low-grade inflammation that will negatively affect the patient's immune response[12].

Richardson et al. (2020), in a study in the United States, showed that 60.7% of patients were obese[39]. Another study in the US revealed higher obesity values (85.6%) and an average BMI of 30.8 kg/m² [10].Study in France identified a significant association of severe obesity (≥35 kg / m^2) with the need for invasive MV (almost 90%)[12].

Table 3. Anthropometric characteristics of patients in the studies.

Author	Country	Study Design	No. Patients	BMI Kg/ m^2	Obesity %	Malnutrition %
Huang et al.[4]	China	Multicenter Retrospective Study	202	26.4	44.4	-
Pedersen et al.[8]	Denmark	Single Center Retrospective Study	16	28.9	18.75	-
Cummings et al.[10]	USA	Prospective Cohort Study	257	30.8	85.6	-
Simonnet et al.[12]	France	Retrospective Cohort Study	124	29.6	75.7	-
Docherty et al.[30]	UK	Prospective Cohort Study	20,133	-	10.5	2.4
Richardson et al.[39]	USA	Retrospective Case Series	5700	-	60.7	-

BMI: Body Mass Index

A clinical trial aimed at exploring risk factors for mortality in the ICU, including obesity and other NCDs, and describing the clinical course and outcomes, including the treatment of acute respiratory failure and other intensive treatments, is being conducted for more accurate conclusions (eg, NCT04425213 registered with ClinicalTrials.gov).

There is currently no standard form of pharmacological and/or nutritional treatment for COVID-19, but satisfactory nutrition will not only help in the maintenance or recovery of the patient's best NS, but may also help in the improvement of the patient's immune response to fight the virus, and in a better prognosis of the disease. A clinical trial to better describe the main clinical characteristics that impact food intake and nutritional status of this population is being done in France (eg, NCT04365816 registered with ClinicalTrials.gov).

The identification of nutritional risk or the presence of malnutrition should be the initial step in the overall assessment of all patients, especially the elderly and individuals suffering from chronic and acute diseases[2]. ESPEN (2020) recommends that poly-morbid patients (with more than two chronic diseases) be automatically characterized as being at high nutritional risk as well as those who have been in ICU for more than 48 hours[2]. There is still no gold standard for nutritional risk assessment in critical patients, some guidelines recommend the use of are Nutrition Risk in Critically Ill Score (NUTRIC score) and Nutritional Risk Screening -2002 (NRS-2002)[2,40], and a clinical trial is currently being conducted for validation of NUTRIC score (eg, NCT04274322 registered with ClinicalTrials.gov). BRASPEN (2020) suggested the elaboration of a protocol in which during the patient's admission process, questions for nutritional screening are already included to avoid the physical contact of the nutritionist with the patients[1].

The use of equipment for nutritional assessment is not being recommended and the evaluation of weight variation of these patients are difficult to be analyzed in the ICU because of fluid administration and rapid wasting of lean tissues[6,7].

Nutritional Therapy

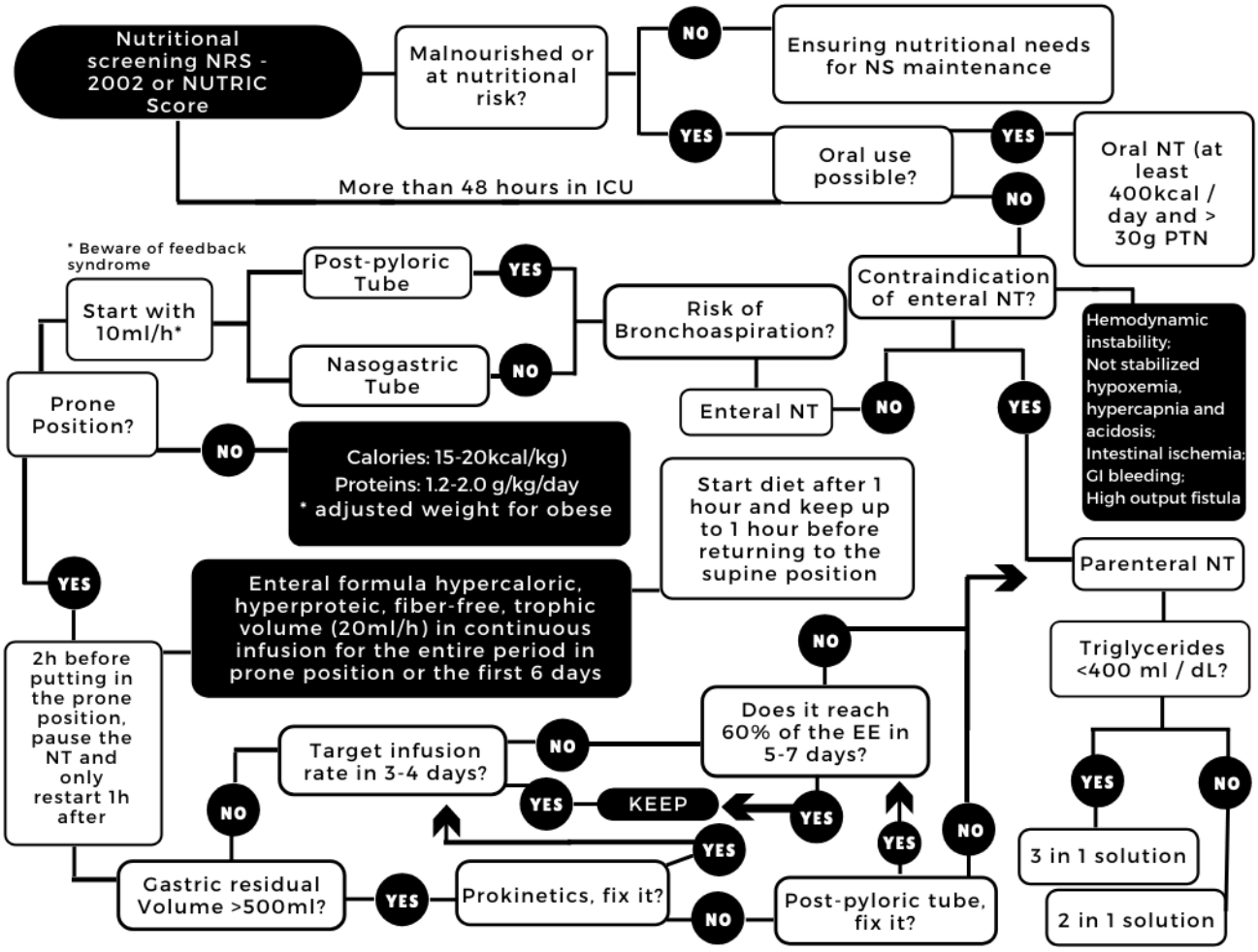
The prevention, diagnosis and treatment of malnutrition should be included in the routine of therapeutic assistance to the patient, due to its effectiveness in reducing complications and improving prognostic[2].

Patients with COVID-19 who require hospitalization in the ICU, most of them need nutritional support, since the greatest reasons for admission to intensive care were due to respiratory failure, consequently, need for MV and inability to eat orally[9]. It is necessary to evaluate possible dysphagia in order to be able to start oral NT, if it is not possible, it should be considered to start enteral NT in order to help preserve the function of the intestinal mucosal barrier and it should

be started within 24 to 48 hours, and ultimately, if all measures have already been taken to maintain the diet in a physiological way and none has worked, parenteral NT of peripheral access should be opted[2,6,7,40]. Patients leaving MV have high rates of dysphagia, and a clinical study is currently being conducted to better assess the prevalence and meet these compensatory treatment needs (eg, NCT04346212 registered with ClinicalTrials.gov), in these cases they are recommended to enteral NT temporarily while undergoing treatment to improve swallowing[2].

A nasogastric tube should be initiated, and the post-pyloric tube should only be considered in cases of gastric intolerance after the use of prokinetics or patients at high risk of aspiration[2,6]. It is suggested that gastric residual volume monitoring should not be used in these patients as an indicator of EN intolerance since the risk of contamination is very high[6,40]. The prone position is not a reason for enteral NT contraindication, only some special care should be taken when offering the diet[1,2,6,7,40]. Patients with stable hypoxemia, and compensated or permissive hypercapnia and acidosis, can start the enteral diet in small doses[1,2,6,7,40]. A flow chart was developed to better understand the recommendations of these patients (Figure 3).

Figure 3. Flow Chart of recommendations for patients with COVID-19 designed by the author.



NS: Nutritional Status. NT: Nutritional Therapy. GI: Gastrointestinal. EE: Energy Expenditure.

Calories and protein

Patients with COVID-19 require a higher energy and protein intake due to the catabolic state of the disease, but when it comes to critical patients, it is ideal that these calories are administered with caution at the beginning of the acute phase of the disease, and depending on the patient's need, then to progress to higher values[1,2,6].

The use of indirect calorimetry to define the energy expenditure, although it is the most recommended, should be avoided in order to reduce the risk of contamination of equipment, the time of the healthcare providers with the infected patient and increase the use of PPE[6.] Predictive equations can be used as well as using VO_2 (Oxygen consumption) from pulmonary arterial catheter or VCO_2 (Carbon dioxide production) derived from the ventilator[6,7]. Pedersen et al. (2020) reported using around 25-30kcal/kg/day in ICU patients who required MV[8].

Given this catabolic state it is important that these patients receive adequate and sufficient nutrition for a better prognosis of the disease. Determining optimal protein needs for critical patients is still controversial, as shown in Table 4. Associated with these recommendations, physical activity is encouraged whenever possible for better recovery and/or maintenance of skeletal muscle, reduce morbidity and prevent anabolic resistance[2,7,40].

Table 4. Energy and protein recommendations for patients with COVID-19

Author	Calories		Proteins
	Acute Phase	After	
Campos et al.[1]	15-20kcal/kg/day	25kcal/kg/day	1.5 – 2.0g/kg/day
Barazzoni et al.[2]	Not exceeding 70% of EE (hypocaloric diet)	27-30kcal/kg/day	1.3g/kg/day
Martindale et al.[6]	15-20kcal/kg/day	-	1.2 – 2.0g/kg/day

EE: Energy Expenditure

Carbohydrates and lipids

BRASPEN (2020) suggests not using formulas with high lipid content and low carbohydrate content to manipulate respiratory coefficient in critical patients with pulmonary dysfunction[1], whereas the ESPEN (2020) recommends a ratio of carbohydrates and lipids of 70:30 for patients without respiratory failure and 50:50 for patients using MV[2]. It is advised that critically ill patients should not exceed 5mg/kg/min of carbohydrates as hyperglycemia and insulin resistance are common in critical patients due to stress[7]. As soon as patients have better GI tolerance and reduced GI symptoms, a fiber-containing formula or supplementation should be considered, since SARS-CoV-2 causes a disturbance in the gut microbiota and the fibers can help in recovery[6].

ASPEN (2020) and ESPEN (2019) revealed no harm in using enteral NT enriched in omega - 3 fatty acids and still believe to bring benefits to these patients, since they play an important role in the modulation of the immune response, and can help improve the patient's response to uncontrolled inflammation caused by SARS-CoV-2, which is called the cytokine storm and which is directly linked to ARDS developed by these patients[6,7]. ESPEN (2019) also recommended the use of 1.0 g/kg/day to 1.5 g/kg/day fat. Glucose monitoring in these patients is indicated, and if they are using parenteral NT, triglyceride monitoring is also recommended[6,7].

Hydratation

It is known that excessive fluid administration in critical patients is associated with worse prognosis, and since a considerable number of patients develop ARDS, which is characterized by an increase in capillary permeability causing pulmonary edema in these patients, the fluid administration should be properly guided and always monitored, since they are even more vulnerable to fluid resuscitation.[41,42]. A positive fluid balance is considered an independent risk factor for mortality since its maintenance for 3 days after admission to the ICU was associated with an increase in mortality[41].

Patients with COVID-19 have high fever, significantly increased respiratory rate (even with respiratory discomfort), lack of appetite, and other conditions that may affect the body water balance, therefore, it is important to adopt a volume management strategy, such as accurate liquid input and output calculations. Hasanin & Mostafa (2020) suggested using real-time measures such as pulse pressure variation, since the use of ultrasound becomes impractical due to the risk of equipment contamination, and clinical evaluation should also be put into practice, such as the observation of lower limb edema, lung edema, and severe hypoxemia, which are good clinical indicators of excess fluid[42].

The use of dense formulas (1.5-2.0 kcal/ml) in these patients is one of the alternatives for a fluid restriction[40]. Pedersen et al. (2020) maintained their patients with fluid restriction to limit fluid accumulation in the lungs[8]. The decision on the amount of fluids is still discussed, and the majority should assess the individual need of each patient.

Micronutrients

Due to malnutrition commonly found among critical patients, it is important to pay attention to the feedback syndrome and always check the levels of phosphorus, magnesium and potassium[2,6,7,40]. Especially serum phosphorus since its deficiency is related to the delay of ventilatory weaning in severe patients[1].

In relation to vitamins A, B complex, C, D and E, and trace elements such as selenium, zinc, iron, magnesium, and copper, these play important and complementary roles in supporting the innate and adaptive immune system[43]. And although vitamins C and D, and zinc have several studies showing their antioxidant and immunoregulatory effect, there are still no recommendations for administration of doses above the Recommended Dietary Allowance (RDA), and should only supplement in case of deficiency (blood or intake level)[2,7].

It is known that deficiencies of these micronutrients negatively affect immune function, decreasing resistance against infections, number of lymphocytes and antibody response, compromising phagocytosis, impairing the antimicrobial role of immune cells, and altering cytokine production[43].

In recent years, the role of high dose vitamin C (3 to 5 g/d), also known as ascorbic acid, in viral infections, sepsis and severe patients has received attention and several researches are underway. In relation to its performance in the immune system, it has been reported that it supports the development and maintenance of physical barriers; acts on the production and activity of antimicrobial proteins; acts on the growth, differentiation and function of leukocytes; stimulates cell motility, chemotaxis and phagocytosis; helps in the protection of neutrophils against oxidative damage due to their antioxidant activity; increases the production of interferon in vitro (antiviral function), also increases the chemotactic and microbial killing capacity of neutrophils and stimulates the proliferation and differentiation of B and T lymphocytes[43]. Recent literature review has reported the possible decrease in susceptibility to respiratory tract infections, such as pneumonia due to SARS-CoV-2, with supplementation of ascorbic acid[43].

ARDS secondary to the virus is characterized by a lesion in the alveolar epithelium with the release of cytokines, which is responsible for the chemotactic attraction of leukocytes. Process that generates reactive oxygen species that will further increase the damage to the epithelium,

causing inflammation[44]. This oxidative stress can be mitigated with the use of antioxidants, so the importance of vitamin C administration[44]. Currently multicenter prospective randomized placebo-controlled study is being conducted with patients infected with SARS-CoV-2 virus, where they are being treated with 24g/day of vitamin C, expecting a clarification about the effect of high doses of vitamin C on the prognosis of patients with COVID-19, especially on respiratory function assessed by ventilation-free days[44].

Some studies have reported an association between low vitamin D concentrations and an increased susceptibility to respiratory infections[43,45,46]. It is believed that vitamin D can modulate the innate and acquired immune system and participate in its maturation[45]. The serum levels of this vitamin tend to decrease with age, in obese patients and in those who have NCDs, which may be an important factor that is linked to higher mortality among these patients with COVID-19[46], so it is also important to check the serum levels of this vitamin in these patients, since supplementation in case of deficiency may favor a better prognostic[2,7].

The special attention given to vitamin D is due to the increasing evidence that its supplementation and restoration normal values in infected patients can improve the immune response by regulating the production of antimicrobial proteins responsible for the elimination of the pathogen and reduce inflammation levels by modulating the production of cytokines, such as TNF-alpha and IL, therefore, are relevant to help in the reduction of infection[43,46]. High doses of vitamin D require caution with calcium supplementation to avoid the risk of hypercalcemia, and addition of magnesium supplementation, since it is believed that magnesium acts as a cofactor of enzymes that metabolize vitamin D in the liver and kidneys[46]. A randomized controlled trial with 475 critically ill adults used a dose of 540,000 IU of vitamin D3 and had a reduction in 28-day mortality but was only benefic with patients that had a previous deficiency[47]. However, another clinical trial with 1360 patients using the same dose did not find an advantage of the high dose of vitamin D3 over 90-day mortality[48].

There are currently three clinical trials being conducted, in USA, UK and Spain, to find out whether there is vitamin D deficiency among individuals infected with SARS-CoV-2 and whether this level affects the prognosis of the disease (eg, NCT04407286, NCT04386044, NCT04403932 registered with ClinicalTrials.gov).

Zinc is important for the maintenance and development of cells that make up the immune system, both innate and adaptive, thus helping in the immune response, in addition to having antioxidant activity[44]. With age, the levels of this mineral decrease, and its deficiency impairs humoral and cell-mediated immunity, which increases the susceptibility to infectious diseases, so

there is a greater propensity of the elderly to contract infections[44]. Calder et al. (2020) commented that the lack of this trace element was associated with respiratory morbidities in children[43].

Given the above, the administration of these micronutrients elucidated could have benefits for the immune system of these patients and help in a better prognosis, however, clinical studies are still needed in humans of different age groups and populations to better substantiate the safe and effective dosage to be used against infections. In the table 5 are some suggestions made by two authors.

Table 5. Micronutrients recommendations for patients with COVID-19

Author	Vitamin C	Vitamin D_3	Zinc
Calder et al.[43]	1-2g/d	2000 IU/day	8-11 mg/day
Grant et al.[2]	-	10,000 IU/d for a few weeks to rapidly raise [25(OH)D] and after 5000 IU/d	-

CONCLUSION

Age and NCDs are considered risk factors for mortality, with SAH and DM being the main ones. The NS of these patients also has a high association with mortality and the use of MV, so the evaluation of the NS should be considered a basic vital sign. Diabetic and hypertensive patients need special attention and care, since it is believed that both diseases are associated with an increased severity of symptoms and complications of SARS-CoV-2 (COVID-19). NT in these patients can improve clinical outcomes, improve treatment, and shorten hospitalization time, as well as reduce complications and mortality, and should be considered as first-line of defense treatment and be more valued in the hospital setting. Although there is no recommendation for supplementation of vitamin C and D and the mineral zinc, these may bring benefits to the immune system of patients affected by this virus and help in a better prognosis of COVID-19, although more studies are still needed to substantiate the dosage. It is important to bring the themes already exposed by some authors to stimulate discussions that might lead to improvements in the standardization of nutritional approaches.

FUNDING

Author states that there has been no funding to carry out this study.

CONFLICTS OF INTERESTS

Author states that there are no conflicts of interest in preparing the manuscript.

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