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Standardized Nutritional Intervention in Patients with COVID-19 Admitted to a Hospital in Bogotá, Colombia

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Summary

Background: Patients with coronavirus disease 2019 (COVID-19) present an increase in oxidative stress, characterized by the production of reactive oxygen species and a concomitant deficiency of antioxidants. There are multiple defense mechanisms including enzymatic scavengers and non-enzymatic molecules (glutathione and vitamins A, C, D, E, and zinc).

Methods: In this observational, cross-sectional, retrospective study, we aimed to describe the clinical behavior of patients hospitalized due to COVID-19 (those treated with a standardized nutritional intervention versus those who received the COVID-19 standard treatment available at the time). A total of 214 medical records of patients hospitalized due to COVID-19 who required nutritional intervention were analyzed. Descriptive analyses of continuous and categorical variables were performed, and an ANOVA test was performed for numerical variables. A logistic regression model and a propensity score matching determined the differences between the matched groups.

Findings: 33·6% of the patients were admitted to the Intensive Care Unit (ICU), 28·5% required invasive mechanical ventilation, and the overall mortality was 19·6%. 44·8% of the patients received the standardized nutritional intervention. There were no statistically significant differences between intervention groups, except for the intervention time, in which the standardized nutritional intervention (days) was identified as a protective factor OR=0·550 (p <0·05; CI=0·324-0·936).

Conclusions: This is the first study in Colombia to consider a standardized nutritional intervention in patients hospitalized due to COVID-19. Despite not being able to meet the primary objectives, controlled experiments must be carried out to determine the role and possible therapeutic effects of micro and macronutrients in patients with COVID-19.

Keywords: Coronavirus infections, COVID-19, nutrition, SARS-CoV-2, vitamin D, ascorbic acid.

Resumen

Antecedentes: los pacientes con enfermedad por coronavirus 2019 (COVID-19) presentan un aumento del estrés oxidativo, caracterizado por la producción de especies reactivas de oxígeno y una deficiencia concomitante de antioxidantes. Existen múltiples mecanismos de defensa que incluyen eliminadores enzimáticos y moléculas no enzimáticas (glutatión y vitaminas A, C, D, E y zinc).

Métodos: En este estudio observacional, transversal y retrospectivo, el objetivo fue describir el comportamiento clínico de los pacientes hospitalizados por COVID-19 (aquellos tratados con una intervención nutricional estandarizada versus aquellos que recibieron el tratamiento estándar COVID-19 disponible en el tiempo). Un total de 214 historias clínicas de los pacientes hospitalizados por COVID-19 que requirieron intervención nutricional. Se realizaron análisis descriptivos de variables continuas y categóricas. Se realizó una prueba de ANOVA para las variables numéricas. Un modelo de regresión logística y un emparejamiento por puntuación de propensión determinaron las diferencias entre los grupos emparejados.

Resultados: el 33,6% de los pacientes ingresaron en la Unidad de Cuidados Intensivos (UCI), el 28,5% requirió ventilación mecánica invasiva y la mortalidad global fue del 19,6%.44 · 8% de los pacientes recibieron la intervención nutricional estandarizada. No hubo diferencias estadísticamente significativas entre los grupos de intervención, excepto por el tiempo de intervención, en el que la intervención nutricional estandarizada (días) se identificó como factor protector OR = 0 · 550 (p <0 · 05; IC = 0 · 324-0 · 936).

Conclusiones: Este es el primer estudio en Colombia que considera una intervención nutricional estandarizada en pacientes hospitalizados por COVID-19. A pesar de no poder alcanzar los objetivos primarios, se deben realizar experimentos controlados para determinar el papel y los posibles efectos terapéuticos de los micro y macronutrientes en pacientes con COVID-19

Palabras clave: Infección por Coronavirus, COVID-19, nutrición, SARS-CoV-2, vitamina D, ácido ascórbico

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Introduction

The management of the infection by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global challenge, as it arises as a new entity with new pathophysiological processes. Given its rapid onset and development, clinical challenges are not yet fully understood. This pandemic infection called coronavirus disease 2019 (COVID-19), produced by the new SARS-CoV-2[1–7], so far does not have an effective therapy. Vitamin D, vitamin C, and zinc are some of its immunity enhancers; there are limited research findings on the antiviral effects of zinc[8–12].

Observational studies have found association between low serum concentrations of 25-hydroxyvitamin D and susceptibility to acute respiratory tract infections. Considering that 25-hydroxyvitamin D influences the production of antimicrobial peptides in response to viral and bacterial stimuli[13–15], a potential mechanism in which vitamin D could induce protection against respiratory pathogens is suggested[16,17]. Insufficient levels of vitamin D and several cellular mechanisms such as replication mediated by papain-like protease (PLpro), the dipeptidyl peptidase-4 receptor (DPP-4/CD26), disruption of mediated M protein, type 1 interferon (IFN) induction, and host recognition progression have been described as progression and mortality factors for COVID-19[18]. Melanoma differentiation-associated gene 5 protein (MDA5) and retinoic acid-inducible gene I protein (RIG-I) have been closely related to the Middle East respiratory syndrome coronavirus (MERS-CoV)[19,20].

Only few studies have evaluated the effect of nutritional interventions on COVID-19, There were a few studies providing direct evidence on associations between zinc, selenium, and vitamin D, and COVID-19. Adequate supply of zinc, selenium, and vitamin D is essential for resistance to other viral infections, immune function, and reduced inflammation. Hence, it is suggested that nutrition intervention securing an adequate status might protect against the novel coronavirus SARS-CoV-2 and mitigate the course of COVID-19[21].

COVID-19 leads to an upregulation of systemic inflammation, as shown by elevated concentrations of proinflammatory cytokines –mainly interleukins (IL) 1, IL-6, IL-10– and tumor necrosis factor (TNF) alpha[22,23]. Likewise, there are reports that confirm the presence of oxidative stress in studies of patients with COVID-19, this is characterized by the production of reactive oxygen species (ROS) and a concomitant deficiency of antioxidants. There are multiple defense mechanisms against ROS including enzymatic scavengers (superoxide dismutase, catalase, and glutathione peroxidase) and non-enzymatic molecules (glutathione and vitamins A, C, and E). The imbalance between the production of ROS and the reserve of antioxidants perpetuates increased damage and inflammation, which can contribute to severe manifestations of COVID-19[24-27].

Therefore, the objective of this study is to describe the clinical behavior of patients hospitalized for COVID-19 treated with supplementation with micronutrients and macronutrients plus nutritional supplementation with hypercaloric and high protein content polymeric formula (standardized nutritional intervention), versus the clinical behavior of those receiving the COVID-19 standard treatment available at the moment in Colombia.

Methods

Participants and Study Design

Retrospective, observational, analytical cross-sectional study. A total of 495 medical records were reviewed. The population analyzed consisted of 214 patients with COVID-19 who were admitted to the hospitalization service and intensive care unit (ICU), and who required supplemental oxygen (O_2) or presented increased inflammatory or poor prognosis markers; in a tertiary health care center in Bogotá (Colombia) between March and August of 2020. Clinical records were reviewed to describe the clinical behavior of patients treated with supplementation with micronutrients and macronutrients (vitamin A 100000 IU/day, vitamin D 2000 IU/day, vitamin C 1000-2000 mg/day, zinc sulfate, syrup 2 mg / ml [15 cc every 12 hours], vitamin E 1000 IU/day) plus nutritional supplementation with hypercaloric and high protein content polymeric formula at a dose of 25-30 Kcal/kg of ideal weight (standardized nutritional intervention), and the clinical behavior of patients receiving the COVID-19 standard treatment available.

Statistical Analysis

A non-probabilistic sampling of medical records of patients hospitalized due to COVID-19 who required the use of supplemental O_2 or who presented increased inflammatory markers was performed. A convenience sampling was used since it was not possible to estimate the sample size due to the unknown prevalence of the disease.

Univariate descriptive analysis of continuous and categorical variables was performed, and measures of central tendency and dispersion were estimated according to the distribution of each variable. Proportions were used for categorical variables. Additionally, a comparative analysis of qualitative variables was performed using Fisher's exact test or chi-squared test between the groups that received and that did not receive standardized nutritional intervention. Secondary, numeric, dependent variables (days of mechanical ventilation and lengths of stay) were analyzed with the ANOVA statistical technique. Wilcoxon test or Student's T-test were used for quantitative variables.

For 204 of the records, a simple logistic regression model and a correlation matrix were performed between the dependent variable "death" and the independent variables. Nagelkerke's R^2, McFadden's R^2, Akaike information criterion (AIC), quantification of standardized coefficients, and the receiver operating characteristic (ROC) curve were performed to evaluate the sensitivity and specificity of the model.

Finally, the sample was matched using propensity scores, controlling confounding variables and limiting potential study biases.

Ethical Considerations

The study protocol was submitted and approved by the Ethics Committee of the institution where it was carried out.

Results

A total of 214 patient records were included in the analysis. The overall mean age was 58·2 years (Standard Deviation [SD] 15·29). 60·2% of the patients were male and 39·7 were female. 53·2% had pre-existing diseases as follows: hypertension (37·8%), diabetes mellitus (21%), chronic obstructive pulmonary disease (COPD) (11·6%), and human immunodeficiency virus (HIV) infection (6%). 95·7% of the patients received antibiotics for treatment of pneumonia. Steroids (Dexamethasone at the doses approved by the RECOVERY study: 6 mg/day) were administered to 40·6% of the patients, hydroxychloroquine was used in 2·8%, colchicine in 2·8%, and lopinavir/ritonavir in 3·27%. 33·6% were admitted to the ICU and 28·5% required invasive mechanical ventilation with an overall mortality of 19·6% (n=42). 44·8% of the patients received standardized nutritional intervention. Clinical and laboratory characteristics are shown in Table 1.

A comparative analysis of the inflammatory and the main outcome variables was performed between the group that received the standardized nutritional intervention and the group that did not (Table 2). Means were compared using the Wilcoxon rank-sum (Mann-Whitney) test.

Considering that the standardized nutritional intervention was predominantly in the patients who were in the ICU, a comparison was made between ICU patients who received the standardized nutritional intervention and patients who did not (Table 3).

Continuous variables that best explain the simple logistic regression model are displayed in Table 4. Additionally, a correlation matrix of continuous variables was calculated, showing moderately high associations (>0·7) between 'Days of Mechanical Ventilation' and 'Standardized Nutritional Intervention Time (days)' (0·742), 'Days of Mechanical Ventilation' and 'Hospital Length of Stay (days)' (0·807), and 'Standardized Nutritional Intervention Time (days)' and 'Hospital Length of Stay (days)' (0·751) (Table 5).

The model used explains 81·7% (McFadden's R^2) and 88·2% (Nagelkerke's R^2) of the outcome 'death' with an AIC of 61·053. The continuous variables 'Hemoglobin (Minimum)', 'Platelets (Minimum)', 'Standardized Nutritional Intervention Time (days)', and 'Hospital Length of Stay (days)' are negatively correlated with the outcome 'death' (Figure 1). Conversely, 'Leucocytes (Maximum)', 'Mechanical Ventilation (days)', 'LDH (Maximum)', and the following categorical variables have positive standardized regression coefficients in relation to the outcome 'death': presence of COPD OR=11·1 (p=0·07; CI=0·76-163·76), presence of Diabetes Mellitus OR=62·558 (p=0·004; CI=3·79-1031·253), ICU Requirement OR=76·2 (p=0·014; CI=2·44-2376·5), and treatment with Standardized Nutritional Intervention OR=33·98 (p=0·027; CI=1·5-768·9) (Figure 1).

The simple logistic regression model had a sensitivity of 87·5%, a specificity of 98·1%, and an Area Under the ROC Curve of 99% (Figure 2).

Finally, the sample was matched using propensity scores to identify the imbalance of baseline characteristics between the patients who received standardized nutritional intervention and patients who did not. A model was generated with 190 matched patients from the sample (95 treated with the standardized nutritional intervention and 95 nontreated), controlling for confounding variables and limiting potential study biases. Graphs of before and after the intervention show the balance of the variables analyzed (Figure 3).

Table 1. Clinical and laboratory characteristics of the overall population.

	Median (Minimum) (IQR)	Median (Maximum) (IQR)
Leucocytes, cells/mm^3 (RV: 4000-11000)	5820·9 (4250 - 7030)	11902 (7315 - 14395)
Lymphocytes, cells/mm^3 (RV: 1000-4000)	815 (380 - 1140)	1602 (1070 - 2045)
Hemoglobin, g/dL (RV: 12-16)	13·2 (11·6 - 15)	15·7 (14·2 - 17·1)
Platelets, x10^3 (RV: 150000-450000)	204909·9 (151000 - 254000)	338066 (251000 - 409000)
CRP, mg/dL (RV: <6)	66·3 (10·26 - 80·2)	208·1 (79·7 - 268)
LDH, U/L (RV: 140-240)	287·4 (212 - 331)	444·6 (306 - 535)
Ferritin, ng/mL (RV: 15-300)	1056 (414 - 1440)	2226·6 (733 - 2741)
D-dimer, FEU/mL (RV: < 500)	548·5 (276 - 612)	2440 (471 - 3626)
Creatinine, mg/dL (RV: 0·5-1·1)	0·8 (0·65 - 1·0)	1·04 (0·85 - 2·21)
	Median	
Troponin, ng/L (RV: < 40)	48·2 (40 - 56·4)	
Hospital Length of Stay, days	10·2 (5 - 12)	
ICU Length of Stay, days	11·6 (7 - 15)	
Standardized Nutritional Intervention Time, days	7·5 (4 - 11)	

CRP=C-reactive protein; FEU=fibrin equivalent units; ICU=intensive care unit; IQR=interquartile range; LDH=lactate dehydrogenase; n=absolute value; RV=reference value.

Table 2. Comparison of clinical and laboratory variables between the intervention and nonintervention groups.

	Intervention Group (n=96)	Non-Intervention Group (n=118)	p-Value
Leucocytes (Minimum), cells/mm^3	5475	5190	0·3077
Leucocytes (Maximum), cells/mm^3	13070	9020	0·0000****
Lymphocytes (Minimum), cells/mm^3	400	910	0·0000****
Lymphocytes (Maximum), cells/mm^3	1395	1575	0·0843
Hemoglobin (Minimum), g/dL	12·3	13·8	0·0006***
Hemoglobin (Maximum), g/dL	15·7	15·6	0·3055
Platelets (Minimum), x10^3	175000	203000	0·0237
Platelets (Maximum), x10^3	285000	285000	0·0000****
CRP (Minimum), mg/dL	36·3	23·41	0·2131
CRP (Maximum), mg/dL	205	121	0·0002***
LDH (Minimum), U/L	297	246	0·0003***
LDH (Maximum), U/L	475·5	345	0·0000****
Ferritin (Minimum), ng/mL	832	645	0·0454*
Ferritin (Maximum), ng/mL	1430	982	0·0018**
D-dimer (Minimum), FEU/mL	378·5	395	0·9210
D-dimer (Maximum), FEU/mL	2112	640	0·0000*
Creatinine (Minimum), mg/dL	0·75	0·85	0·1689
Creatinine (Maximum), mg/dL	1·1	0·98	0·1336
Troponin, ng/L	40	40	0·0004***
Mechanical Ventilation, days	11	4	0·0035**
ICU Length of Stay, days	11·5	5	0·0017**
Hospital Length of Stay, days	11·5	6	0·0000****

CRP=C-reactive protein; FEU=fibrin equivalent units; ICU=intensive care unit; LDH=lactate dehydrogenase; n=absolute value.
*=p <0·05; **=p <0·005; ***=p <0·001; ****=p <0·0001.

Table 3. Comparison of clinical and laboratory variables between the intervention and nonintervention groups of patients admitted to the ICU.

	Intervention Group (n=51)	Non-Intervention Group (n=17)	p-Value
Age	59	64	0·3705
Leucocytes (Minimum), cells/mm^3	6300	8380	0·0644
Leucocytes (Maximum), cells/mm^3	17480	14240	0·0767
Lymphocytes (Minimum), cells/mm^3	320	530	0·0002**
Lymphocytes (Maximum), cells/mm^3	1320	1260	0·4658
Hemoglobin (Minimum), g/dL	11·8	12·9	0·3601
Hemoglobin (Maximum), g/dL	16	14·7	0·1057
Platelets (Minimum), x10^3	150000	177000	0·5912
Platelets (Maximum), x10^3	377000	275000	0·0026*
CRP (Minimum), mg/dL	38·9	37	0·9189
CRP (Maximum), mg/dL	266	202·5	0·0698
LDH (Minimum), U/L	322	332	0·3375
LDH (Maximum), U/L	546	534·5	0·8097
Ferritin (Minimum), ng/mL	1076	615	0·1062
Ferritin (Maximum), ng/mL	1517	1383	0·6138
D-dimer (Minimum), FEU/mL	431	586	0·1960
D-dimer (Maximum), FEU/mL	3372	2930	0·2411
Creatinine (Minimum), mg/dL	0·75	0·77	0·7359
Creatinine (Maximum), mg/dL	1·43	1·24	0·2562
Mechanical Ventilation, days	11	4	0·0035*
ICU Length of Stay, days	11·5	5	0·0017*
Hospital Length of Stay, days	18	7	0·0011*

CRP=C-reactive protein; FEU=fibrin equivalent units; ICU=intensive care unit; LDH=lactate dehydrogenase; n=absolute value.

*=p <0·005; **=p <0·001.

Table 4. Continuous variables included in the simple logistic regression.

	Median	SD
Leucocytes (Maximum), cells/ mm3	11925·373	6504·362
Hemoglobin (Minimum), g/dL	12·469	2·274
Platelets (Minimum), x103	202146·716	84871·202
Mechanical Ventilation, days	3·461	6·463
Hospital Length of Stay, days	10·377	8·299
LDH (Maximum), U/L	445·191	198·101

LDH=lactate dehydrogenase; SD=standard deviation.

Discussion

In recent months, multiple therapeutic strategies have been implemented (some of them scientifically based and other empirically based) to address the COVID-19 pandemic; these include antiretroviral drugs, corticosteroids, and immunomodulators. Empirical treatments have been used due to the urgency of the situation and the lack of current clinical evidence. However, it has been recently documented how vitamin D levels above 38 ng/mL are related to positive outcomes in respiratory infections, especially the one caused by SARS-CoV-2, [18,28–32] and its possible role in the prevention of contagion and reduction in the severity of symptoms.

The limitations of this study include being a retrospective study, with a small number of patients, and in which the primary objectives could not be demonstrated. Likewise, the doses of some interventions may have been insufficient at the time the intervention was designed, and we still do not have a conclusive guide about the micronutrient doses that should be implemented for this disease. However, this study shows how some interventions should be implemented early (regardless of the severity of the infection) to get a better effect and a longer follow-up time.

The use of a 'loading dose' of vitamin D has been reported to reach a target level where a plasmatic concentration of 30 ng/mL can be achieved by using different dosing regimens (daily, weekly, biweekly, monthly). In some studies, interest has been focused on patients with elevated inflammatory markers (e.g., obesity or overweight) and it has been established that the necessary contribution should be 2 to 3 times higher than the established for the general population[18,28–32]. In our study, doses considered standard or minimum required (daily) were used. However, not having the baseline or postintervention serum vitamin D levels is an important limitation since it was not possible to establish the exact doses of this supplementation and thus define an individualized regimen according to those levels.

Strategies such as the one suggested by Grant et al.[23], with a dose of 10000 IU/day for one month to rapidly reach the goal of levels between 40 and 60 ng/mL, and then continue with 5000 IU/day for a few more weeks have been proposed. However, in our study, because it is a standardized nutritional intervention in hospitalized patients, much lower doses (2000 IU/ day) and in a much shorter time were used. Minimum requirements of daily doses of vitamin D and limitations due to the administration techniques (especially in patients who required ICU stay and invasive mechanical ventilation) must be considered.

The proposed level of high doses is striking, neglecting possible adverse effects. Some studies show that a dose of 10000 IU/day for 4-6 months lacks toxicity[32–34], so the dose could have

Table 5. Correlation matrix of continuous variables.

	Leucocytes (Maximum)	Hb (Minimum)	Platelets (Minimum)	Mechanical Ventilation (days)	Standardized Nutritional Intervention Time (days)	Hospital Length of Stay (days)	LDH (Maximum)
Leucocytes (Maximum)	**1·000**	-0·306	-0·285	0·633	0·519	0·499	0·509
Hb (Minimum)		**1·000**	0·196	-0·446	-0·426	-0·452	-0·205
Platelets (Minimum)			**1·000**	-0·275	-0·179	-0·174	-0·265
Mechanical Ventilation (days)				**1·000**	0·742	0·807	0·366
Standardized Nutritional Intervention Time (days)					**1·000**	0·751	0·350
Hospital Length of Stay (days)						**1·000**	0·254
LDH (Maximum)							**1·000**

Hb=hemoglobin; LDH=lactate dehydrogenase.

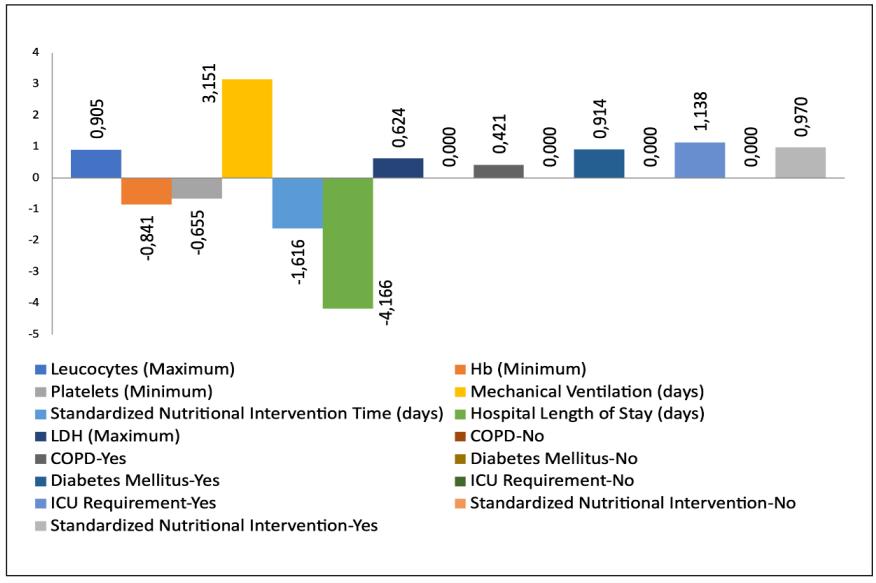

Figure 1. Standardized regression coefficients of variables against the outcome "death".
COPD=chronic obstructive pulmonary disease; Hb=hemoglobin; ICU=intensive care unit; LDH=lactate dehydrogenase.

been increased for patients with mild to moderate infections that did not require an ICU stay or even in those who required an ICU stay but did not require invasive mechanical ventilation; considering what was mentioned regarding the administration technique and the pharmaceutical forms of vitamin D.

It is known that vitamin D inhibits the S-phase kinase-associated protein 2 (SKP2), which plays a central role in the viral replication mechanism of SARS-CoV-2[35,36], and uses the blockade of autophagy for its accelerated replication and infectivity. The virus induces SKP2, which inactivates Beclin-1 (an essential component of the autophagic process)[36]. Unfortunately, at the moment, the molecular mechanisms are not clear and there is no evidence in our country to determine the beneficial effects of the standardized nutritional intervention at a molecular level.

One of the striking findings is that the variable of 'Standardized Nutritional Intervention (days)' acts as a protective factor against the outcome variable OR=0·550 (p <0·05; CI=0·324-0·936). This generates even more hypotheses regarding nutritional supplementation prior to infection or in the early stages of it, considering that a longer time of exposure to it may promote favorable outcomes. The pre-existing conditions of the patients included in the analysis behaved as risk factors that increased the probability of death. COPD and Diabetes Mellitus significantly increased the risk of dying by 11 and 63 times, respectively. Another significantly associated risk factor was the ICU Length of Stay, which increased the risk of death by 76 times.

Among the results, higher levels of inflammatory markers were found in patients who received the standardized nutritional intervention and this group had more severe symptoms of infection. However, the nutritional intervention not necessarily caused this or increased mortality. Clinical trials or controlled studies should be carried out to determine the reduction of inflammatory markers as has been demonstrated in other settings of patients in the ICU or with infections different than viral[37–39].

Regarding other micronutrients (such as vitamin A, C, E and trace elements such as zinc) and their possible role in viral diseases, no recommendations can be made up to this point on their implementation since it was not possible to demonstrate a reduction in inflammatory markers in the group that received this intervention. However, patients with upper respiratory infections caused by other types of respiratory viruses have shown a shorter duration of symptoms[9–12].

Contrary to what was expected, mortality was much higher in the intervention group; however, this could be a result of the study design, its potential selection and information biases,

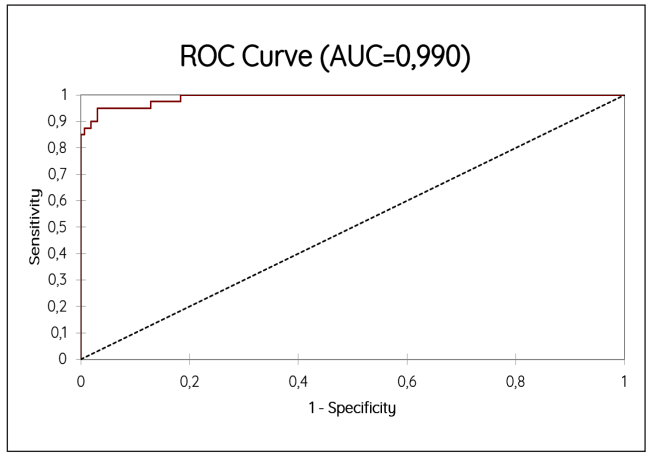

Figure 2. ROC curve.
AUC=area under the curve; ROC=receiver operating characteristic.

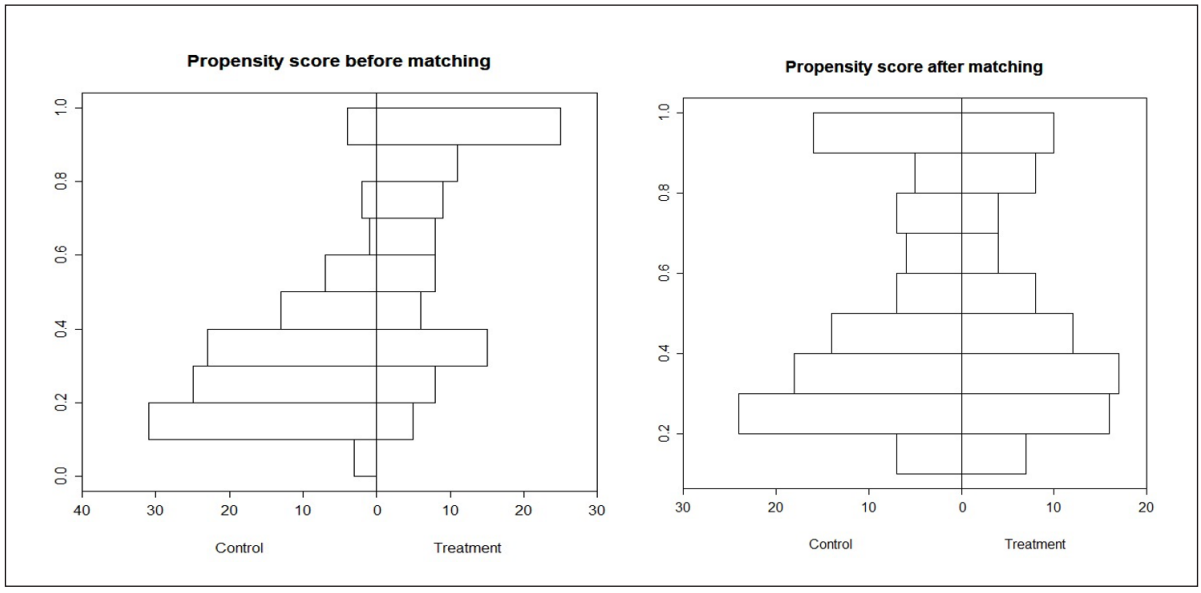

Figure 3. Propensity score matching before and after standardized nutritional intervention.

the nonrandomization, and the complexity of inferring or demonstrate a reduction in mortality using this methodological design. We consider that nutritional interventions should not be dismissed for the following reasons: their biological rationale and potential low rate of adverse effects or toxicity, and the need of an adequate caloric intake and maintenance of gastrointestinal trophism in critically ill patients as a complement to other interventions carried out in the ICU.

This is the first study in Colombia to consider a standardized nutritional intervention in patients hospitalized for COVID-19. Despite not being able to demonstrate the primary objectives and considering that there is no proven therapy so far for this disease, controlled studies must be carried out to determine the real role of micro and macronutrients, their doses, and potential therapeutic effects in patients with COVID-19 or other viral infections.

Table 6. Model parameters (DEATH variable).

	Value	Standard Error	Wald Chi-Square	Pr >Chi^2	Wald Lower Limit (95%)	Wald Upper Limit (95%)	Odds Ratio	Odds Ratio Lower Limit (95%)	Odds Ratio Upper Limit (95%)
Interception	4.969	4.593	1.170	0.279	-4.034	13.972			
Leucocytes (Maximum), cells/mm^3	0.000	0.000	2.750	0.097	0.000	0.001	1.000	1.000	1.001
Hemoglobin (Minimum), g/dL	-0.672	0.295	5.191	0.023	-1.251	-0.094	0.511	0.286	0.910
Platelets (Minimum), x10^3	0.000	0.000	3.356	0.067	0.000	0.000	1.000	1.000	1.000
Mechanical Ventilation, days	0.887	0.255	12.123	0.000	0.388	1.386	2.427	1.473	3.998
Standardized Nutritional Intervention Time, days	-0.597	0.271	4.863	0.027	-1.128	-0.066	0.550	0.324	0.936
Hospital Length of Stay, days	-0.913	0.295	9.570	0.002	-1.491	-0.335	0.401	0.225	0.716
LDH (Maximum), U/L	0.006	0.004	2.664	0.103	-0.001	0.013	1.006	0.999	1.013
COPD-No	0.000	0.000							
COPD-Yes	2.414	1.369	3.109	0.078	-0.270	5.098	11.183	0.764	163.766
Diabetes Mellitus-No	0.000	0.000							
Diabetes Mellitus-Yes	4.136	1.430	8.368	0.004	1.334	6.939	62.558	3.795	1031.253
ICU Requirement-No	0.000	0.000							
ICU Requirement -Yes	4.334	1.755	6.101	0.014	0.895	7.773	76.267	2.448	2376.527
Standardized Nutritional Intervention -No	0.000	0.000							
Standardized Nutritional Intervention -Yes	3.526	1.591	4.909	0.027	0.407	6.645	33.984	1.502	768.913

COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; LDH=lactate dehydrogenase.

Table 7. Standardized coefficients (DEATH variable).

	Value	Standard Error	Wald Chi-Square	Pr >Chi²	Wald Lower Limit (95%)	Wald Upper Limit (95%)
Leucocytes (Maximum), cells/mm³	0.905	0.546	2.750	0.097	-0.165	1.975
Hemoglobin (Minimum), g/dL	-0.841	0.369	5.191	0.023	-1.564	-0.118
Platelets (Minimum), x10³	-0.655	0.357	3.356	0.067	-1.355	0.046
Mechanical Ventilation, days	3.151	0.905	12.123	0.000	1.377	4.925
Standardized Nutritional Intervention Time, days	-1.616	0.733	4.863	0.027	-3.051	-0.180
Hospital Length of Stay, days	-4.166	1.347	9.570	0.002	-6.806	-1.527
LDH (Maximum), U/L	0.624	0.382	2.664	0.103	-0.125	1.372
COPD-No	0.000	0.000				
COPD-Yes	0.421	0.239	3.109	0.078	-0.047	0.889
Diabetes Mellitus-No	0.000	0.000				
Diabetes Mellitus-Yes	0.914	0.316	8.368	0.004	0.295	1.533
ICU Requirement-No	0.000	0.000				
ICU Requirement -Yes	1.138	0.461	6.101	0.014	0.235	2.041
Standardized Nutritional Intervention -No	0.000	0.000				
Standardized Nutritional Intervention -Yes	0.970	0.438	4.909	0.027	0.112	1.827

COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; LDH=lactate dehydrogenase.

Pearson's Correlation Test

Table 8. Descriptive analysis.

	Observations	Observations with lost data	Observations without lost data	Minimum	Maximum	Mean	SD
Leucocytes (Maximum), cells/mm³	188	0	188	1100.000	44200.0	11752.745	6330.240
Hemoglobin (Minimum), g/dL	188	0	188	5.800	17.500	12.408	2.249
Platelets (Minimum), x10³	188	0	188	130.000	492000.0	203584.734	84908.626
LDH (Maximum), U/L	188	0	188	142.000	1800.0	449.048	199.345
Mechanical Ventilation, days	188	0	188	0.000	36.0	3.447	6.454
Standardized Nutritional Intervention Time, days	188	0	188	0.000	18.0	3.532	4.988
Hospital Length of Stay, days	188	0	188	0.000	58.0	10.383	8.408

LDH=lactate dehydrogenase; SD=standard deviation.

Table 9. Correlation Matrix (Pearson).

	Leucocytes (Maximum)	Hemoglobin (Minimum)	Platelets (Minimum)	LDH (Maximum)	Mechanical Ventilation (days)	Standardized Nutritional Intervention Time (days)	Hospital Length of Stay (days)
Leucocytes (Maximum)	1	-0.275	-0.271	0.506	0.604	0.538	0.474
Hemoglobin (Minimum)	-0.275	1	0.190	-0.186	-0.420	-0.416	-0.423
Platelets (Minimum)	-0.271	0.190	1	-0.280	-0.260	-0.160	-0.156
LDH (Maximum)	0.506	-0.186	-0.280	1	0.361	0.365	0.248
Mechanical Ventilation (days)	0.604	-0.420	-0.260	0.361	1	0.764	0.800
Standardized Nutritional Intervention Time (days)	0.538	-0.416	-0.160	0.365	0.764	1	0.759
Hospital Length of Stay (days)	0.474	-0.423	-0.156	0.248	0.800	0.759	1

LDH=lactate dehydrogenase.
Note: All values in bold style are different than 0 and have an alpha significance level =0.05.

Table 10. *p*-Values.

	Leucocytes (Maximum)	Hemoglobin (Minimum)	Platelets (Minimum)	LDH (Maximum)	Mechanical Ventilation (days)	Standardized Nutritional Intervention Time (days)	Hospital Length of Stay (days)
Leucocytes (Maximum)	0	0.000	0.000	0.000	0.000	0.000	0.000
Hemoglobin (Minimum)	0.000	0	0.009	0.011	<0.0001	<0.0001	<0.0001
Platelets (Minimum)	0.000	0.009	0	0.000	0.000	0.028	0.033
LDH (Maximum)	<0.0001	0.011	0.000	0	<0.0001	<0.0001	0.001
Mechanical Ventilation (days)	<0.0001	<0.0001	0.000	<0.0001	0	<0.0001	<0.0001
Standardized Nutritional Intervention Time (days)	<0.0001	<0.0001	0.028	<0.0001	<0.0001	0	<0.0001
Hospital Length of Stay (days)	<0.0001	<0.0001	0.033	0.001	<0.0001	<0.0001	0

LDH=lactate dehydrogenase.
Note: All values in bold style are different than 0 and have an alpha significance level =0.05.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this article.

Conflict of interest. The authors declare that the revision was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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