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# Efectos de la inmunonutrición sobre los niveles de albúmina sérica, IL-6 y TNF-α en pacientes con COVID-19: un ensayo clínico aleatorizado, controlado, doble ciego

# Effects of immunonutrition on serum albumin, IL-6, and TNF-α levels in patients with COVID-19: a randomized controlled double-blind clinical trial

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# Effects of immunonutrition on serum albumin, IL-6, and TNF-α levels in patients with COVID-19: a randomized controlled double-blind clinical trial

*Efectos de la inmunonutrición sobre los niveles de albúmina sérica, IL-6 y TNF-α en pacientes con COVID-19: un ensayo clínico aleatorizado, controlado y doble ciego*

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**ABSTRACT**

**Background and objectives:** many specialized immunonutrient formulas are available, with an emphasis on combining arginine, omega 3 fatty acids, and nucleotides. These nutrients can reduce the inflammatory pattern, with an increased contribution to resolving infections. Considering the inflammatory catharsis resulting from COVID-19, this study aimed to evaluate the effect of immunonutrition on serum albumin, IL-6, and TNF-α levels in patients with COVID-19.

**Materials and methods:** a randomized double-blind clinical trial conducted in 2020 in Salvador, Bahia, Brazil. Adult patients diagnosed with COVID-19 were randomized to receive a standard hyperproteic

normocaloric supplement (control) or a supplement enriched with immunonutrients (experiment) for a period of 07 days. The participants were monitored for a period of 08 days, including the assessment of risk and nutritional status, and collection of blood samples to evaluate albumin, IL-6, and TNF-α.

**Results**: 70 patients were included in the study. 64 were randomly allocated to receive an immunonutrient diet or a standard control diet. The nutritional diagnosis was 27.6 (± 0.8) kg/m² and the nutritional risk was 41.9 %. In the experiment group, there was an average increase in albumin to 0.84 (± 0.65) mg/dL, while in the control group this increase was of 0.21 (± 0.52) mg/dL. Regarding the IL-6 doses, there was a reduction both in the experiment group (-257.27 ± 448.89 pg/ml) and in the control group (-142.75 ± 253.29 pg/ml). When comparing the difference in TNF-α levels, a reduction was observed in the experiment group (-3.72 ± 5.98 pg/ml), while an increase in the control group (5.33 ± 10.48 pg/ml) was observed.

**Conclusions:** the use of an oral supplement enriched with immunonutrients seems to be able to reduce the IL-6 and TNF-α serum levels and increase serum albumin levels.

**Keywords**: Immunonutrition. Albumin. IL-6. TNF-α. COVID-19.

**RESUMEN**

**Antecedentes y objetivos**: se encuentran disponibles muchas fórmulas de inmunonutrientes especializadas, con énfasis en la combinación de arginina, ácidos grasos omega 3 y nucleótidos. Estos nutrientes pueden reducir el patrón inflamatorio, con una mayor contribución a la resolución de infecciones. Considerando la catarsis inflamatoria resultante de la COVID-19, este estudio tuvo como objetivo evaluar el efecto de la inmunonutrición sobre los niveles de albúmina sérica, IL-6 y TNF-α en pacientes con COVID-19.

**Materiales y métodos**: ensayo clínico aleatorizado, doble ciego, realizado en 2020 en Salvador, Bahía, Brasil. Los pacientes adultos diagnosticados con COVID-19 fueron aleatorizados para recibir un suplemento normocalórico hiperproteico estándar (control) o un suplemento enriquecido con inmunonutrientes (experimento) por un período de 07 días. Los participantes fueron monitoreados por un período de 08 días, incluyendo evaluación de riesgo y estado nutricional, y recolección de muestras de sangre para evaluación de albúmina, IL-6 y TNF-α.

**Resultados**: se incluyeron en el estudio 70 pacientes. 64 fueron asignados al azar para recibir una dieta de inmunonutrientes o una dieta de control estándar. El diagnóstico nutricional fue de 27,6 (± 0,8) kg/m² y el riesgo nutricional fue del 41,9 %. En el grupo experimental, hubo un aumento promedio de albúmina a 0,84 (± 0,65) mg/dL, mientras que en el grupo control este aumento fue de 0,21 (± 0,52) mg/dL. En cuanto a las dosis de IL-6, hubo una reducción tanto en el grupo experimental (-257,27 ± 448,89 pg/ml) como en el grupo control (-142,75 ± 253,29 pg/ml). Al comparar la diferencia en los niveles de TNF-α, se observó una reducción en el grupo experimental (-3,72 ± 5,98 pg/ml), mientras que se observó un aumento en el grupo control (5,33 ± 10,48 pg/ml).

**Conclusiones**: el uso de un suplemento oral enriquecido con inmunonutrientes parece ser capaz de reducir los niveles séricos de IL-6 y TNF-α y aumentar los niveles de albúmina sérica.

**Palabras clave**: Inmunonutrición. Albúmina. IL-6. TNF-α. COVID-19.

## INTRODUCTION

During the COVID-19 pandemic, there were combat fronts that sought to reduce contagion through the use of personal protective equipment (PPE), hygiene, distancing policies, and social blockade

(lockdown). In addition to these measures, there was also an attempt to mitigate the morbidity and mortality of the clinical repercussions caused to infected individuals, mainly through vaccines and life support equipment and medication (1). In this regard, studies have been proposed which better understand the genomic, morphology and molecular identification of the etiologic agent, the dynamics of transmission and entry into the host, intracellular replication, clinical manifestations, risk factors, and host immune response (1,2).

These exacerbated clinical repercussions are mainly consequences of the SARS-CoV-2 virus (4) connecting with the angiotensinogen converting enzyme II (ECAII) and its subsequent entry into host cells (5). After this invasion, the viruses have their molecular pattern associated with pathogens recognized by pattern recognition receptors (RRP), located on the plasma membrane of the cells, and which recruit general antiviral regimens, mediated by the stimulation of some interferons (especially the pro-inflammatory ones, TNF-α and IFN-γ) and by the secretion of chemokines that attract more cells from the innate response (polymorphonuclear leukocytes, dendritic cells, monocytes, and NK cells) (1,4,5).

As the response depends on how efficient the immune system is, the clinical variations of this disease range from asymptomatic patients to death, the main risk factors being age, endocrine metabolic and cardiovascular comorbidities, as well as immunosuppression and underlying inflammatory diseases (4).

In this context, under conditions of severe acute inflammatory stress, there are changes in biochemical markers, such as a drop in serum albumin and an increase in IL-6 and TNF-α, which corroborate the cytokine storm and the subsequent injury to tissues through thrombotic actions to disinhibit coagulation related to oxidative stress and platelet activation (6-9).

With the benefit of inflammatory modulation, reduction of oxidative stress, and expansion of plasma volume through therapy in sepsis, cirrhosis, and obviously, ARDS, these advantages influenced the

search for therapies that could improve these changes in COVID-19 infections, while maintaining an acceptable level of efficacy and safety. Thus, an approach was adopted, which consisted of administering albumin and using drugs aiming at the immune system. The literature established counterpoints to the inconvenience of direct albumin infusion and the use of these drugs, such as their side effects, costs, and adverse events (10,11).

It is evident that, for the inflammatory state to recover, the immune system must undergo a modulated activation, which is co-dependent on the nutrients available as an energy source, and on structural molecules, such as ω-3, nicotinamide, non-essential amino acids such as arginine and glutamine, as well as vitamins (12). In this respect, many specialized formulas with added immunonutrients are available. Among others, these formulas contain a combination of arginine, ω-3, and nucleotides. Hence, these nutrients can reduce the inflammatory pattern, leading to a consequent increase in contributing to resolving infections (13-16).

Studies on immunomodulators involving ω-3, nucleotides, arginine and their influence on serum albumin are still scarce, especially with regard to non-surgical patients with non-neoplastic diseases or when they are administered orally. In view of the above, this study aims to evaluate the effect of immunonutrition on serum levels of albumin, IL-6 and TNF-α in patients with COVID-19.

## MATERIALS AND METHODS

This is a phase IV, longitudinal, prospective, analytical, controlled, randomized clinical trial with a 1:1 allocation, and double-blind. The study was conducted at a hospital specialized in the care of patients diagnosed with COVID-19, in the city of Salvador, Bahia, Brazil.

All patients (the total number of beds available) admitted to the infirmary ward, diagnosed with COVID-19 over six months, covering the period from July to December 2020, and who met the eligibility criteria for this study, were studied. The patients were monitored

prospectively up to a maximum period of 8 days.

Adult patients, aged between 18 and 65 years, diagnosed with COVID-19 through molecular examination (RT-PCR), with a pervious gastrointestinal tract, using an oral diet, and who were not on mechanical ventilation or did not need to be admitted to the ICU, were considered eligible for the study. Regarding the exclusion criteria, patients who were pregnant; submitted to the use of artificial nutrition in the 15 days prior to being included in this study; patients allergic to any component of the diets used; with severe hyperglycemia (> 180 mg/dl) or hypertriglyceridemia (> 400 mg/dl); with previous gastrointestinal diseases (surgical resections, malabsorption syndromes, inflammatory bowel diseases, persistent paralytic ileus, upper gastrointestinal bleeding or severe acute pancreatitis); with immunosuppression states defined by neutropenia, myelodysplastic syndromes, congenital immunodeficiency or acquired immunodeficiency syndrome (AIDS), immunosuppressive therapies in the last 3 months, systemic chemotherapy in the last 3 months, autologous bone marrow transplant in the last year, halogen bone marrow transplantation in the last 2 years, or the existence of graft-versus-host disease (DEVH); with advanced chronic diseases (Child-Pugh stage C, heart failure grade IV, functional stage-IV chronic lung failure, terminal degenerative neurological processes, neoplasms in remission or in progression on treatment); with processes with short life expectancy, including end-stage chronic kidney disease; with acute processes that determine short survival as a shock of any etiology with multiple organ dysfunction refractory to therapy within the first 48 hours or after cardiopulmonary resuscitation with severe neurological damage within 72 hours.

Randomization was simple, carried out by means of a simple, random draw, on a website called Research Randomizer (17). After applying the inclusion and exclusion criteria, forty-three patients were eventually randomized to receive standard hyperproteic normocaloric supplement (control) or supplement enriched with immunonutrients

(experiment) at a ratio of 1:1, for a period of 7 days. The supplements were blinded to both patients and researchers.

A pilot study was performed with a sample of 10 % of the total population so as to align with the research protocol. In order to analyze assessment error, the kappa coefficient was used, which assesses the agreement between the evaluators. The kappa index was < 0.80, which was considered to be a good correlation (18).

The participants in the control group received 2 200 ml units of normocaloric, hyperproteic oral nutritional supplement, without the addition of any immunonutrition component (Nutren Senior®, Nestlé), distributed over 24 hours. This supplement provided, for each 100 ml, 98 kcal, 8.0 g of protein, 9.4 g of carbohydrates, 3.2 g of fats, with no fiber or lactose.

The participants in the experiment group received 2 200 ml units of normocaloric, hyperproteic oral nutritional supplement, with the addition of L-arginine, nucleotides and ω-3 fatty acids (Impact®, Nestlé), distributed over 24 hours. This supplement provided, for each 100 ml, 109 kcal, 6.5 g of protein, 14 g of carbohydrates, 2.8 g of fats, with no fiber or lactose.

Over the period of 7 days, the supplements were dispensed in 300 ml, disposable, capped cups without any identification as to the name of the product. The delivery began on the day the participant was included in the study organized by the hospital's Clinical Nutrition team, through the maids, who also did not know which product they were delivering.

The drug treatment established to control the symptoms caused by the SARS-CoV-2 infection followed the institutional protocol and was prescribed equally to all patients.

The participants were monitored by the researchers for a period of 8 days, including assessment of risk and nutritional status, collection of blood samples for biochemical and immunological tests, and recording of possible clinical complications.

Regarding assessing the risk of their nutritional status, the

participants were evaluated by the researchers on the day they were included in the study (D0). The Nutritional Risk Screening 2002 (NRS 2002) tool was used for nutritional risk assessment (19). This instrument is the method recommended by the European Society for Clinical Nutrition (ESPEN) (19,20). It is also the most suitable nutritional risk screening method for hospitalized patients in Brazil.

In addition, all participants had their weight and height recorded, barefoot and in light clothing. They were placed at the center of a digital scale (Welmy-W300A®, São Paulo, Brazil), in upright position, in a way that both feet distributed their weight. Body weight was recorded in kg, in three digits (00.0 kg), immediately after its reading. As for the height recording, using a stadiometer, each participant was positioned barefoot, with no accessories on the head, erect, with their arms extended alongside the body, head held high, looking at a fixed point at eye level. The height was recorded in meters, using three digits (0.00 meters).

The participants also underwent blood sampling from a peripheral vein (basilic or cephalic) on D0 and after the period of supplement use on the 8th day (D8). These samples were identified and sent to the clinical analysis laboratory of the Immunology Service of the Federal University of Bahia (UFBA), for the measurement of albumin, IL-6 and TNF-α serum levels.

Albumin was quantified using the colorimetric method, values ≥ 3.5 g/dL without depletion and values lower than 3.5 g/dL with depletion were considered.

In order to determine IL-6 and TNF-α, serum samples were measured by an immunoenzymatic assay, by means of the enzyme-linked immunosorbent assay (ELISA) method, using blood plasma, as per manufacturer's instructions.

Throughout data collection, hospital medical records were searched so as to complement the data collected by the researchers.

It should be noted that on D0, patients were admitted, anthropometric measurements were carried out and the blood sample

was collected. The diets were administered between D1 and D7, and on D8, the anthropometric measurements were re-verified, and the blood sample collected.

The main outcome was the assessment of changes in albumin, IL-6, and TNF-α serum levels. The secondary outcomes of the study, on the other hand, were the patients' nutritional risk and nutritional status according to BMI.

The researchers did not need to report any adverse events to the Research Ethics Committee (CEP) and, consequently, no use of the supplement was temporarily suspended, nor did any research subject withdraw from the study.

The data were analyzed by means of descriptive and analytical statistics, consistent with relative and absolute frequency. The Shapiro-Wilk test and histogram inspection were applied in order to verify the normality of the continuous variables. According to the type of variable and normality, statistical tests were applied to verify the difference between the groups. Among the nominal qualitative variables, the following stand out: gender, race, and nutritional risk. As for quantitative variables, the following are distinctive: age, height, weight, BMI, and albumin, IL-6, and TNF-α serum levels.

Regarding the statistical analysis, Student's t test was applied for normal variables and the Mann-Whitney's U test was applied for non-parametric variables, by means of the mean and standard deviation, in order to verify the difference between the comparison groups. Categorical covariates were evaluated using the Pearson's chi-square test.

In order to quantify how likely the treatment proposed is to be effective, relative risk (RR) and relative risk reduction (RRR) were calculated. All relative risk calculations were performed in a 2 x 2 table. When calculating the RR, the *p*-value was obtained using Fisher's exact test. For all analyses, a confidence level of 95.0 % ($p < 0.05$) was adopted. The power of the study was of 99.64 %.

The data were tabulated and analyzed on Stata/MP 16.0 for

Windows (StataCorp LLC®, Texas, USA), licensed by the Bahia State University (UNEB) affiliated to the Laboratory for Teaching, Research and Extension in Collective Health (LEPESC/UNEB).

This research was registered with CEP/UNEB under CAAE No. 31801820.0.0000.0057 and approved by opinion No. 4,031,187. Brazilian Resolution No. 466/2012, which attends to ethics and bioethics in research involving human beings and the principles of the Declaration of Helsinki, were respected.

The clinical trial was also registered in the Brazilian Registry of Clinical Trials (REBEC) under UTN No. U1111-1252-3270.

## RESULTS

From July to December 2020, a total of 70 patients were included in the study. Sixty-four out of 70 were randomly allocated to receive an immunonutrient diet or a standard control diet (Fig. 1). After randomization and the onset of diet administration, 10 and 11 patients, respectively from the control and experiment groups, were lost from follow-up. No patient withdrew consent or experienced serious adverse events during the study follow-up period.

The average age of the participants in the present study was 41.5 (± 1.9) years, 60.5 % of whom were male. Regarding the nutritional diagnosis, measured by the body mass index, it amounted to 27.6 (± 0.8) kg/m², classified as overweight. Nutritional risk, on the other hand, was considered high in 41.9 % of the sample studied.

Serum albumin levels on D0 were, on average, of 3.58 (± 0.62) mg/dL and of 3.22 (± 0.53) mg/dL in the control and experiment groups, respectively. There was a statistically significant difference between these dosages in the groups ($p < 0.05$). On D8, serum albumin averages were of 3.79 (± 0.71) mg/dL and 4.06 (± 0.46) mg/dL in the control and experiment groups, respectively. There was no difference between group averages for this dosage ($p = 0.07$).

The IL-6 dosage on D0, on the other hand, presented an average of 313.41 (± 301.15) pg/ml and 351.72 (± 473.03) pg/ml for the control

and experiment groups, respectively. There was no statistically significant difference between these dosages in the groups ($p$ = 0.57). On D8, the average IL-6 serum levels were 170.66 (± 174.98) pg/ml and 94.45 (± 70.59) pg/ml for the control and experiment groups, respectively. In this case, there was also no statistically significant difference between the groups ($p$ = 0.19).

Regarding the TNF-α levels on D0, an average of 2.75 (± 4.04) pg/ml and 11.27 (± 14.86) pg/ml were observed for the control and experiment groups, respectively. There was no statistically significant difference between these dosages in the groups ($p$ = 0.15). On D8, the average TNF-α dosage was 8.08 (± 9.59) pg/ml and 7.54 (± 12.15) pg/ml for the control and experiment groups, respectively. In this case, there was also no statistically significant difference between the groups ($p$ = 0.45).

The average difference between serum levels measured between D0 and D8 in each group is shown in table I. In the experiment group, there was an average increase in albumin to 0.84 (± 0.65) mg/dL, while in the control group this increase was of 0.21 (± 0.52) mg/dL. There was statistical significance between the differences in the reduction ($p$ < 0.01).

Regarding the IL-6 doses, there was a reduction both in the experiment group (-257.27 ± 448.89 pg/ml) and in the control group (-142.75 ± 253.29 pg/ml). Although the reduction was greater in the experiment group, there was no statistical significance when comparing the differences in the averages between the groups ($p$ = 0.90).

When comparing the difference in TNF-α levels, a reduction was observed in the experiment group (-3.72 ± 5.98 pg/ml), while an increase in the control group (5.33 ± 10.48 pg/ml) was observed. In this case, the TNF-α changes between the groups proved to be statistically significant ($p$ < 0.01).

Table II shows the results regarding the efficacy of the immunonutrient diet in increasing serum albumin levels and reducing

IL-6 and TNF-α dosage by 30 % or more compared to the same possibility using the control diet. The increase in albumin occurred in 95.5 % of those who received an immunonutrient diet, while 4.5 % of those who received the standard diet showed the same decrease.

Therefore, it can be highlighted that the group that received immunonutrition had 11.52 (95 % CI, 1.63-81.63) more risk of raising albumin by more than 30 % than the control group. In other words, the use of a hyperproteic supplement enriched with arginine, ω-3 and nucleotides allowed for a 2,022 % albumin increase when compared to the control group ($p < 0.001$).

As for the IL-6 dosage, 6 (54.5 %) participants in the experimental group had decreased serum levels, while 7 (58.3 %) of those who received a control diet had the same outcome. Thus, the use of immunonutrients proved to represent 0.93 (95 % CI, 0.45-1.92) more risk of decreasing these levels in the bloodstream when compared to the use of standard supplements. However, this result was not statistically significant ($p = 0.85$).

Regarding TNF-α reduction, 4 (36.4 %) participants in the experiment group decreased their serum levels, while 1 (8.3 %) of those who received a control diet had the same outcome. Thus, the use of immunonutrients proved to represent a 4.36 (95 % CI, 0.57-33.31) higher risk of decreasing these levels in the bloodstream when compared to the use of standard supplements. However, this result was also not statistically significant ($p = 0.10$).

## DISCUSSION

According to the authors' own knowledge, this appears to be the first study to investigate the use of immunomodulators in patients diagnosed with COVID-19.

Although scientific output on COVID-19 has been vast since the genesis of the pandemic to the present day, there are still some gaps in the field. Inflammatory markers are known to be highly associated with the severity of COVID-19 (21-23). In this regard, several studies

were very important for understanding the clinical evolution of the disease (22,23). On the other hand, clinical trials on immunonutrition and its role in the SARS-COV-19 pathogenesis are still very scarce.

The findings of this study demonstrate that immunonutrition, in the form of a supplement containing arginine, ω-3, and nucleotides appears to be capable of increasing serum albumin levels, as well as reducing IL-6 and TNF-α by 30 % when compared to the control group.

In a prospective cohort conducted in Italy, from March 2020 to June 2021, patients hospitalized with COVID-19 at a university hospital that dosed serum albumin both upon admission and after prolonged hospitalization, had hypoalbuminemia. They concluded that lower serum albumin levels upon admission were related to a higher risk of severe respiratory failure, death, and extended length of stay (24).

Another randomized double-blind clinical study evaluated the effect of ω-3 supplementation in critically ill patients with COVID-19, with a sample of 128 infected patients. The intervention lasted 14 days, with albumin dosed. It should be noted that there was no statistical significance between the control and intervention groups. However, ω-3 supplementation improved the levels of various respiratory and renal parameters (25).

In this context, our study showed significant reductions in albumin, thus it appears that the use of immunonutrients increased the serum levels of this protein. Of course, the indirect effect of ω-3 can improve blood circulation and endothelial function while maintaining vessel integrity and satisfactory oncotic pressure. Arginine, on the other hand, which acts in protein synthesis, provides vasodilation and nitrogen retention, which indirectly promote albumin homeostasis.

Although this study did not find any statistical significance between the decreases in IL-6 for the group that received immunonutrition, it should be noted that in the experiment group there was a greater reduction when compared to the control one. Arginine is believed to aid in the production of nitric oxide (NO), through the enzyme nitric

oxide synthetase (NOS). It is worth noting that NO acts as an important regulator of processes in the cardiovascular system and as an antagonist of smooth muscle contractions, in addition to inhibiting platelet activation. Ω-3 fatty acids, on the other hand, act mainly on the bronchopulmonary system and seem to be able to improve lung compliance. Nevertheless, immunonutrient supplementation seems to reduce unstable molecules, as well as reactive oxygen and pro-inflammatory cytokines such as TNF-α and IL-6 (26,27). Robust studies must be performed to better predict the plausibility proposed.

Regarding the TNF, there was also a greater reduction in the intervention group when compared to the control group. A randomized, controlled non-inferiority trial conducted between November 2017 and November 2018 in Poland, aiming at investigating the role of immunonutrition in the inflammatory response in patients undergoing preoperative colorectal cancer surgery, found that the use of supplementation enriched with immunonutrients in the preoperative period may be able to influence the inflammatory response, when compared to the control group (28). Modulation of cytokine production by immunonutrition is well established in the literature and medical practice, commonly used in surgical procedures, with important scientific evidence (28-30).

The present study had some limitations. First, the loss of follow-up, both in the experiment and in the control groups, may have impacted the study results. Nevertheless, the losses were proportionately equal in both groups studied.

On the other hand, our study used a supplement containing ready-to-consume immunonutrients, so it was not possible to analyze the effects of arginine, ω-3, and nucleotides separately. Finally, another limitation was the fact that it was impossible to withdraw the drugs used. However, as it was a hospital with a pre-defined care profile, the medication protocol adopted was standardized, which possibly mitigated the impacts on the study results.

## CONCLUSION

The present study shows that the use of an oral supplement enriched with immunonutrients seems to be able to reduce IL-6 and TNF-α serum levels and increase serum albumin levels.

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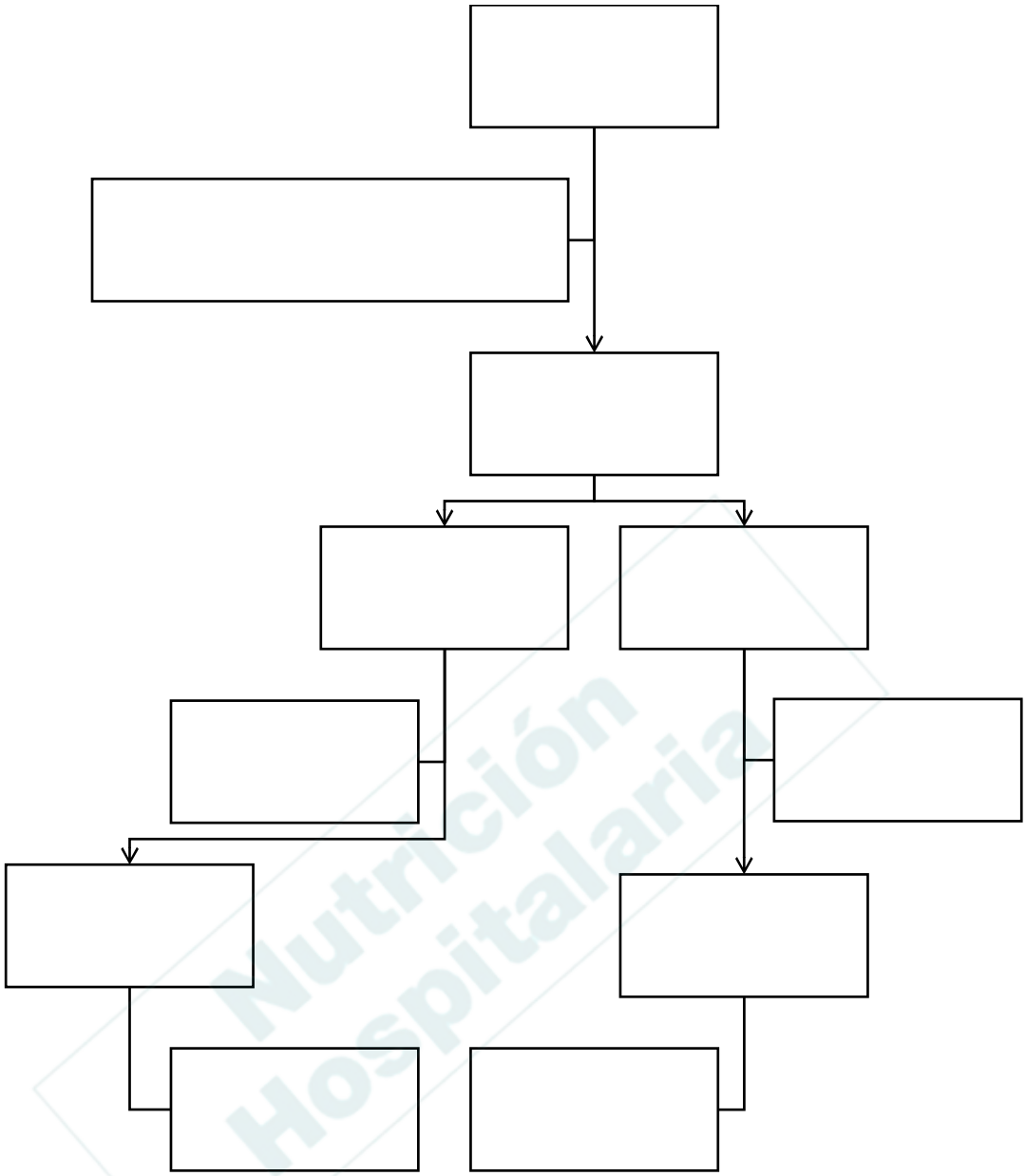

Figure 1. Recruitment, randomization and follow-up.

Table I. Main outcome (difference between albumin, IL-6 and TNF-α doses, during the participant follow-up period with a molecular diagnosis of COVID-19), Salvador, Brazil, 2020

| **Variables** | **Experiment group** | | **Control group** | | ***p*-value** |
|---|---|---|---|---|---|
| | *D0* | *Δ* | *D0* | *Δ* | |
| Albumin | 3.22 (± 0.53) | 0.84 (± 0.65) | 3.58 (± 0.62) | 0.21 (± 0.52) | 0.07 |
| IL-6 | 351.72 (± 473.03) | -257.27 (± 448.89) | 313.41 (± 301.15) | -142.75 (± 253.29) | 0.90 |
| TNF-α | 11.27 (± 14.86) | -3.72 (± 5.98) | 2.75 (± 4.04) | 5.33 (± 10.48) | < 0.01 |

D0: baseline; D8: 8$^{th}$ day after using the supplements; Δ: difference between D8 and D0 dosages.

Table II. Efficacy in reducing the incidence of primary outcomes among participants with a molecular diagnosis of COVID-19, Salvador, Brazil, 2020

| | **Event *n* ( %)** | | **RR (95 % CI)** | **RRR** | ***p*-value** |
|---|---|---|---|---|---|
| | **Experiment** | **Control** | | | |
| Albumin (Increase ≥ 30 %) | 11 (52.4) | 1 (4.5) | 11.52 (1.63-81.63) | -2,022 | < 0.001 |
| IL-6 (Reduction ≥ 30 %) | 6 (54.5) | 7 (58.3) | 0.93 (0.45-1.92) | 1 | 0.85 |
| TNF-α (Reduction ≥ 30 %) | 4 (36.4) | 1 (8.3) | 4.36 (0.57-33.31) | -338 | 0.10 |
| RR: relative risk; RRR: relative risk reduction; CI: confidence interval; PCR: C-reactive protein. | | | | | |