EFFECT OF A NUTRITIONAL SUPPORT SYSTEM TO INCREASE SURVIVAL AND REDUCE MORTALITY IN PATIENTS WITH COVID-19 IN STAGE III AND COMORBIDITIES —— A BLINDED RANDOMIZED CONTROLLED CLINICAL TRIAL

STATISTICAL ANALYSIS PLAN (SAP)

Section 1: Administrative information

1. Title and Trial registration

Item 1a: Descriptive title

"EFFECT OF A NUTRITIONAL SUPPORT SYSTEM TO INCREASE SURVIVAL AND REDUCE MORTALITY IN PATIENTS WITH COVID-19 IN STAGE III AND COMORBIDITIES —— A BLINDED RANDOMIZED CONTROLLED CLINICAL TRIAL". STATISTICAL ANALYSIS PLAN.

Item 1b: Trial registration number

Protocol identification number: 202036.

CONBIOETICA-15-CEI-004-20160729.

Clinical Trials identifier: NCT04507867.

2. SAP Version

Item 2: SAP version number with dates

Version: 1.0. Date: July 28, 2021.

3. Protocol Version

Item 3: Reference to version of Protocol being used

This document has been written based on information contained in the study protocol version 1, dated July 2020.

4. SAP Revisions - revision history with justification and timing

Item 4a/4b/4c: SAP Revision History

SAP revision history.

Protocol version	Updated SAP version no.	Section number changed	Description of and reason for change	Date changed
1.0	1.0			

5. Roles and Responsibility - non-signatory names and contribution

Item 5: Names, affiliations, and roles of SAP contributors

Conceptualization: F.L-M; data curation: LC. A-B, A.GP, D.G-T and G.C-C; formal analysis: F.L-M, A.I-A, G.C-C and LC. A-B; funding acquisition: F.L-M, A.I; investigation: F.L-M, LC. A-B, A.GP, D.G-T and G.C-C; methodology: F.L-M, LC. A-B, A.GP, D.G-T and G.C-C; project administration: F.L-M, LC. A-B, A.GP and D.G-T; resources: LC. A-B, A.GP, D.G-T and M.M-G; supervision: F.L-M; writing - review and editing: F.L-M, A.I, LC. A-B, A.GP, D.G-T and G.C-C. All authors have read and agreed to the published version of the manuscript.

6. Roles and Responsibility – signatures

Item 6a: Signature of person writing the SAP

Fernando Leal-Martinez, M.D., MSc., DSc. (F.L-M).

Antonio Ibarra, M.D., MSc., DSc. *(A.I).*

Marco Montell-García, M.D. *(M.M-G).*

Lorena C. Abarca-Bernal, M.D. *(LC. A-B).*

Alejandra Garcia-Perez, M.D. *(A.GP)*.

Dinnaru Gonzalez-Tolosa, M.D. *(D.G-T)*.

Georgina Cruz-Cázares *(G.C-C)*.

Item 6b: Signature of senior statistician responsible

Senior statistician: Antonio Ibarra, M.D., MSc., DSc. *(A.I)*.

Item 6c: Signature of chief investigator / clinical lead

Principal Investigator/Clinical lead: M.D., MSc., DSc. Fernando Leal-Martinez. *(F.L-M)*

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6. Roles and Responsibility - signatures

Names	Roles and Responsibility	Signature
Fernando Leal-Martinez *M.D., MSc.,* DSc.	Conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing-review, and editing.	
Antonio Ibarra *M.D., MSc., DSc.*	Formal analysis, funding acquisition, review, and editing.	
Lorena C. Abarca-Bernal *M.D.*	Data curation, formal analysis, investigation, methodology, project administration resources, writing-review, and editing.	
Alejandra Garcia-Perez *M.D.*	Data curation, formal analysis, investigation, methodology, project administration resources, writing-review, and editing.	
Dinnaru Gonzalez-Tolosa *M.D.*	Data curation, investigation, methodology, project administration resources, writing-review, and editing.	

Georgina Cruz-Cázares	Data curation, formal analysis, investigation, methodology, writing-review, and editing.	
Marco Montell-García *M.D*	Hospital Resources.	

Section 2: INTRODUCTION

7. Background and rationale of study (optional)

Item 7: Synopsis of trial background and rationale including brief description of research question and brief justification for undertaking the trial

COVID-19 is a rapidly spreading disease with a high hospital mortality rate. It has caused the collapse of health systems worldwide due to the lack of specific treatments to reduce complications and mortality. Nutrition has only been considered as an energetic support even though malnutrition has been associated with a higher risk of mortality. Therefore, it is important to investigate a nutritional support system that helps to reduce mortality and increase survival in patients with COVID-19 in stage III and comorbidities to a greater degree than with conventional nutritional treatment.

8. Objectives and hypotheses.

Item 8: Description of specific objectives or hypotheses

The primary objective is to determine the effectiveness of the Nutritional Support System (NSS) on increasing survival and reducing mortality in patients with COVID-19 in stage III and comorbidities compared to conventional nutritional therapy.

Secondary objectives:

1. To evaluate the effect of the NSS on progression to intubation, evolution to extubation, and mortality in intubated patients.
2. To evaluate the effect of NSS on clinical and biochemical changes among patients.
3. To evaluate the effect of NSS on the biochemical status associated with overall mortality.

Study hypotheses

The null hypothesis: The nutritional support system will not reduce mortality or increase survival in patients with COVID-19 in stage III and comorbidities compared to conventional nutritional therapy.

Research hypothesis: The nutritional support system will reduce mortality and increase survival in patients with COVID-19 in stage III and comorbidities compared to conventional nutritional treatment.

Section 3: Trial Methods

9. Trial design - description of trial design

Ítem 9: Brief description of trial design including type of trial

Randomized, blinded, controlled clinical trial. Selected patients will be randomized into two groups: 1) Control Group (CG) will receive the hospital diet and 2) Intervention Group (IG) will receive the hospital diet and the NSS. Treatment allocation will have a 1:1 ratio.

10. Randomization

Randomization will be performed using a raffle; eighty numbers are to be placed (from 1 to 80). Subsequently, each number will be randomly selected from the raffle and sequentially assigned to one of the two groups, until reaching 40 numbers per group. Each number represents the moment the patient enrolls. In this way, once the recruitment starts, the first patient will be assigned number one; the second will be number two, and so on.

11. Sample size

Item 11: Full details of the same size calculation or alternatively reference to sample size calculation in protocol (instead of replication in SAP).

The sample size will be calculated using the formula: $n = \frac{z^2\, p\, q}{e^2}$, where: 95% confidence level (z = 1.96), p = 0.975, q = 0.025, with a margin of error of 5% (e = 0.05), obtaining 38 patients per group for the sample.

12. Framework

Ítem 12: Superiority, equivalence or non-inferiority trial hypothesis testing framework, and wick comparisons will be presented on this basis.

The effect of NSS in increasing survival and reducing mortality in patients with COVID-19 will be demonstrated by the significant superiority of IG over CG.

13. Statistical Interim analyses and stopping guidance

Item 13a: Information on interim analyses specifying what interim analyses will be carried out and listing of time points:

No interim analyses are planned in the study.

Item 13b: Any planned adjustment of the significance level due to interim analysis:

No adjustment of the significant level due to interim analysis are planned.

13c. Details of guidelines for stopping a trial early:

The following points are considered in planning the early stopping of the study:

1. That the intervention causes serious adverse effects in patients generating insecurity in its application.
2. That the investigators detect improbable, ineffective, or extreme differences between the CG and the IG.

3. New information emerges that raises serious safety issues or convincingly answers to the main question.

14. Timing of final analysis

Item 14: Timing of final analysis e.g all outcome analyzed collectively or timing stratified by planned length of follow-up

The follow-up will start in September 2020 until the established sample is met.

The last day of the study for each patient is going to be 40 days after hospital discharge.

Statistical analysis of clinical and biochemical variables will be performed on baseline, day three, hospital discharge and day 40. Analysis of overall survival and mortality will be performed from baseline to day 40 or patient death. Progression of patients to Mechanical Ventilation Assistance (MVA) will be performed from baseline until the last patient is intubated, mortality in patients with MVA will be performed from intubation to day 40 or death.

15. Timing of outcome assessments

Item 15: Time points at which the outcomes are measured

Survival and Mortality

- Overall survival and mortality: performed from baseline to day 40 or patient death.
- Progression of patients to Mechanical Ventilation Assistance (MVA): performed from baseline until the last patient is intubated.
- Mortality in patients with MVA: performed from intubation to day 40 or death.

Clinical and biochemical variables

- Delivered oxygen flow and maintenance of SpO2 > 90%: will be analyzed at baseline and day three.
- qSOFA scale: will be analyzed at baseline compared with day three.

- Gastrointestinal function (average of gastrointestinal movements, abdominal distension, and Bristol scale): will be analyzed at baseline compared with day three.
- Laboratory parameters: will be analyzed at baseline, day three and hospital discharge.
- PHQ-9: will be analyzed at baseline and hospital discharge.

Follow-up at day 40

- SpO2 without supplemental oxygen, use of home oxygen upon hospital discharge, days of supplemental oxygen use, post-covid syndrome, decrease in body weight: all will be analyzed from hospital discharge until day 40.

Section 4: Statistical Principles

16. Confidence intervals and p-values

Item 16: Level of statistical significance

P values ≤0.05 will be considered indicative of statistical significance in all cases. P values will be one-sided.

Item 17: Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

This study will not analyze data that required multiplicity tests. To avoid type 1 error, an alpha value of 5% will be used (considering $p < 0.05$ significant), aberrant data will be eliminated, validated tests applicable to the study variables will be defined and established, specific inclusion criteria will be implemented for homogenization of the sample to avoid bias variables, and a specific sample size calculation will be performed.

Item 18: Confidence intervals (CI) to be reported

All the confidence intervals presented will be 95%.

19. Adherence and Protocol Deviations

Item 19a: Definition of adherence to the intervention and how this is assessed including extent of exposure.

The intervention will consist of : 1) 2 envelopes of NSS taken in a period of less than 15 minutes (without the presence of vomiting) after morning and afternoon meals during the first 21 days or until hospital discharge, 2) 1 capsule of *Saccharomyces Bourlardii* before the NSS and 1 capsule with the second envelope for 6 days or until hospital discharge, 3) intramuscular B complex; 1 ampoule after meals for 5 days or at hospital discharge.

Adherence to treatment will be established as taking more than 95% of the NSS and not fasting for 2 consecutive days.

Item 19b: Description of how adherence to the intervention will be presented

The intervention will be applied by the research team, who will be responsible for the application and collection of data, which will be reported in daily formats in the morning and afternoon shifts.

The clinical investigators are going to prepare each supplement, administer, and witness each intake of the NSS, registering the time as well as any immediate side effects such as vomiting, bloating, and abdominal pain.

Item 19c: Definition of protocol deviation for the trial:

The following will be considered major violations of the predefined protocol that could affect the primary outcome:

- Failure to meet the inclusion criteria.
- Failure to sign the informed consent letter.
- Failure to follow protocol procedures that specifically relate to the primary endpoints of safety or efficacy of the study.

Item 19d: Description of which protocol deviations will be summarized (may include details of whether deviation is major or minor and impact on analysis populations and approach to summarizing protocol deviations e.g. number and type of protocol deviation, per group).

Deviations from the protocol will be classified before concluding the study. The number and percentage of patients with major and minor deviations from the protocol will be summarized by study group with details of the type of deviation provided. The patients included in the analysis data set will be used as the denominator to calculate the percentages.

20. Analysis populations

Item 20: Definition of analysis populations e.g intention-to-treat (ITT), per-protocol, complete case, safety.

Patients with COVID-19 stage III, both sexes between 30 and 75 years with comorbidities (DM2, SAH, BMI 25-40). We will select 80 patients divided into two groups: CG (hospital diet), and IG (hospital diet + NSS).

Both groups will be analyzed for 1) survival and mortality, 2) clinical and biochemical variables, and 3) follow-up 40 days after discharge.

Section 5: Trial Population

21. Screening Data

Item 21: Reporting of screening data (if collected) to described representativeness of trial sample

The screening data report and screening data will be included in the manuscript in the following sections:

1. Consort figure based on CONSORT 2010 guidelines.
2. Table showing demographic analysis of the patients.

3. Table showing baseline results.
4. Summary of screening data described in the first part of the results section.

22. Eligibility

Item 22: Summary of eligibility criteria

The inclusion and exclusion criteria will be indicated in the methods section. The selected and non-selected patients will be included in the CONSORT diagram, where the causes of ineligibility will be indicated.

23. Recruitment

Item 23: Information to be included in the CONSORT flow diagram

A CONSORT flow diagram will be used that will include the following study and patient information:

- Assessed for eligibility at screening.
- Eligible at screening.
- Not meeting inclusion criteria including patients with respiratory rate disturbance (>30 bpm), glycemia >250 mg/dl, Glomerular filtration rate (GFR) < 60 ml/kg/m^2, platelets level (<150 10 ^3 /L), concomitant autoimmune diseases (hypothyroidism, rheumatoid arthritis, atopic dermatitis), and/or respiratory disorders (bronchial asthma, obstructive sleep apnea syndrome, chronic lung lesions).
- Declined to participate.
- Randomization of all patients.
- Assignation of 40 patients to CG (received hospital diet and hospital treatment) and 40 patients to IG (received intervention - NSS, probiotics, B complex, hospital diet, and hospital treatment).

- Report of incidents.
- Variables analyzed in both groups with their evaluation periods.
- Primary outcomes.

24. Withdrawal/ Follow-up - level of withdrawal

Item 24a: Level of withdrawal e.g. from intervention and/or from follow up

The withdrawal levels that could be present in the study are listed as follows:

1. Participants can withdraw from the intervention and follow-up stops but the information collected is considered as data.
2. If patients decide to withdraw from follow-up, they are asked to allow us to use the data collected to date.
3. If a patient does not allow his/her data to be analyzed, they will not be considered in the analysis.
4. If the patient presents secondary reactions or does not adequately follow the treatment, they should leave the study and their data will be considered for the analysis.
5. Data from patients who die will be considered in the analysis.

Item 24b: Timing of withdrawal/lost to follow up data

The report of withdrawals and losses will be established in the CONSORT diagram, Kaplan-Meier curves, and primary outcomes section, where the timing of withdrawals will be mentioned, as well as the analysis and number of deaths.

Item 24c: Reasons and details of how withdrawal/lost to follow up data will be presented

Reasons for patients deciding to withdraw and deaths from COVID-19 complications will be presented on the CONSORT diagram, Kaplan-Meier curves, and in the primary outcomes section.

25. Baseline patient characteristics

Item 25a: List of baseline characteristics to be summarized

The clinical characteristics, demographic analysis and baseline values will be presented in tables. Details of the randomization will be mentioned in the methods section.

Item 25b: Details of how baseline characteristics will be descriptively summarized

Categorical data will be summarized by numbers and percentages. Normality tests will be applied to evaluate the distribution of the data. If the continuous data present a normal distribution, they will be assumed by mean, SD, and range. If they do not present a normal distribution, they will be summarized with the median and the IQR. Minimum and maximum values will also be presented for continuous data. Statistical significance tests will be performed between both groups in the baseline to rule out significant differences.

Section 6: Analysis

26. Outcomes definitions

Item 26a: Specification of outcomes and timings

Primary outcomes

- Overall mortality and survival will be assessed from the baseline to day 40.
- Progression to AVM will be assessed from baseline until the last patient is intubated.
- Mortality and survival in intubated patients will be assessed from baseline to day 40.

These results will be included in the results section of the manuscript.

Secondary Outcomes

Administration of supplemental oxygen flow, oxygen saturation (spO2), qSOFA scale, and gastrointestinal function will be assessed by comparing at baseline to day 3 intragroup and intergroup. The PHQ-9 test will be assessed at baseline and at discharge between both groups.

These results will be included in the secondary outcomes section of the manuscript. Analysis of the association of baseline biochemical parameters and mortality will be considered in a table and in the secondary outcomes section of the manuscript.

The spO2 without supplemental oxygen requirement, home supplemental oxygen requirement, post COVID syndrome, and body weight at day 40 will be analyzed between both groups in a table.

These results are included in the follow-up section of the manuscript.

Item 26b: Specific measurement and units

- SpO2 (%)
- Mortality (days of death)
- Kilocalories (kcal / day)
- PHQ9 (pts).
- Temperature (ºC).
- Hemoglobin (g / dL).
- Mean corpuscular volume (fL).
- Mean corpuscular hemoglobin concentration (g / dL).
- Leukocytes (10 ^ 3 / µL).
- Neutrophils (%).
- Platelets (10 ^ 3 / µL).
- Glucose (mg / dL).
- Total cholesterol (mg / dL).
- Triglycerides (mg / dL).
- Aspartate aminotransferase (U /L).
- Alanine aminotransferase (U / L).
- Albumin (g/dL).
- Blood Urea Nitrogen (mg / dL).
- Urea (mg / dL).
- Creatinine (mg / dL).
- Glomerular filtration rate
- Ferritin (ng / mL)
- Fibrinogen (mg / dL)
- C-reactive protein (mg / L)
- Dimer-D (ng / mL)
- Procalcitonin (ng / mL)

27. Analysis methods

To consider statistical significance in the results, a value of $p < 0.05$ will be used.

The analysis of the primary and secondary outcomes is shown in the following table.

Variable	Outcome	Timing	Normality test	Summary results	Parametric test	Nonparametric test	Categorical data test	Analysis type
Overall survival	Primary	40 days follow-up	-	Kaplan-Meier	-	-	Log Rank	Intergrupal
Progression to intubation	Primary	until the last patient is intubated	-	Kaplan-Meier	-	-	Log Rank	Intergrupal
Survival in intubated	Primary	40 days follow-up	-	Kaplan-Meier	-	-	Log Rank	Intergrupal
Oxygen flow (L)	Secondary	Basal vs day 3	Shapiro-Wilk	Mean and SD	Paired T test	Wilcoxon	-	Intragrupal
qSOFA (pts)	Secondary	Basal vs day 3	Shapiro-Wilk	Mean and SD	Paired T test	Wilcoxon	-	Intragrupal
Defecations per day (No.)	Secondary	Day 3	Shapiro-Wilk	Mean and SD	Unpaired T test	Mann Whitney	-	Intergrupal
Distension (Yes/No)	Secondary	Day 3	Shapiro-Wilk	Proportions	-	-	Fisher	Intergrupal
PHQ-9 (pts)	Secondary	Basal vs Discharge	Shapiro-Wilk	Mean and SD	Paired T test	Wilcoxon	-	Intragrupal
Oxygen saturation >90%	Secondary	Day 3	Shapiro-Wilk	Proportion	-	-	Fisher	Intergrupal
Hydric balance	Secondary	Day 3	Shapiro-Wilk	Mean and SD	Unpaired T test	Mann Whitney	-	Intergrupal
Bristol scale “normal”	Secondary	Day 3	Shapiro-Wilk	Proportion	-	-	Fisher	Intergrupal
Saturation without supplemental O2	Secondary	Day 40	Shapiro-Wilk	Mean and SD	Unpaired T test	Mann Whitney	-	Intergrupal
Need for supplemental O2 at home	Secondary	Day 40	Shapiro-Wilk	Proportion	-	-	Fisher	Intergrupal
Days of supplemental O2 use at home	Secondary	Day 40	Shapiro-Wilk	Mean and SD	Unpaired T test	Mann Whitney	-	Intergrupal
Postcovid syndrome	Secondary	Day 40	Shapiro-Wilk	Proportion	-	-	Fisher	Intergrupal
Decrease in weight	Secondary	Day 40	Shapiro-Wilk	Proportion	-	-	Fisher	Intergrupal
Gastrointestinal symptoms	Secondary	Day 40	Shapiro-Wilk	Proportion	-	-	Fisher	Intergrupal

28. Missing data

Item 28: Missing data-reporting and assumptions/statistical methods to handle missing data (multiple imputation)

Statistical methods to handle missing data will not be performed.

30. Harms

Item 30: Sufficient detail provided on summarizing harms

The probable adverse effects that could occur are intolerance to formula components, allergic reactions, constipation, headache, rash, and gastrointestinal disturbances. If constipation occurs, the amount of water in patients will be adjusted.

31. Statistical Software

Item 31: Details of statistical packages to be used to carry out analyses (optional)

The analysis will be carried out using Graphpad Prism version 6 software and SPSS Statistics 25 version.

32. References

Item 32a: References to be provided for non-standard statistical methods.

- LCTC - Declaración de SAP [Internet]. Org.uk. Available at: https://www.lctc.org.uk/SAP-Statement
- Welch RW, Antoine JM, Berta JL, Bub A, de Vries J, Guarner F, et al. Guidelines for the design, conduct, and reporting of human intervention studies to assess the health benefits of food. Br J Nutr. 2011; 106 Suppl 2 (S2): S3-15.

Item 32b: Reference to Data Management Plan

- LCTC - Declaración de SAP [Internet]. Org.uk. Available at: https://www.lctc.org.uk/SAP-Statement

- Welch RW, Antoine JM, Berta JL, Bub A, de Vries J, Guarner F, et al. Guidelines for the design, conduct, and reporting of human intervention studies to assess the health benefits of food. Br J Nutr. 2011; 106 Suppl 2 (S2): S3-15.

Item 32c: Reference to the Trial Master File and Statistical Master File

- LCTC - Declaración de SAP [Internet]. Org.uk. Available at: https://www.lctc.org.uk/SAP-Statement
- Welch RW, Antoine JM, Berta JL, Bub A, de Vries J, Guarner F, et al. Guidelines for the design, conduct, and reporting of human intervention studies to assess the health benefits of food. Br J Nutr. 2011; 106 Suppl 2 (S2): S3-15.

Item 32d: Reference to other Standard Operating procedures or documents.

- LCTC - Declaración de SAP [Internet]. Org.uk. Available at: https://www.lctc.org.uk/SAP-Statement
- Welch RW, Antoine JM, Berta JL, Bub A, de Vries J, Guarner F, et al. Guidelines for the design, conduct, and reporting of human intervention studies to assess the health benefits of food. Br J Nutr. 2011; 106 Suppl 2 (S2): S3-15.

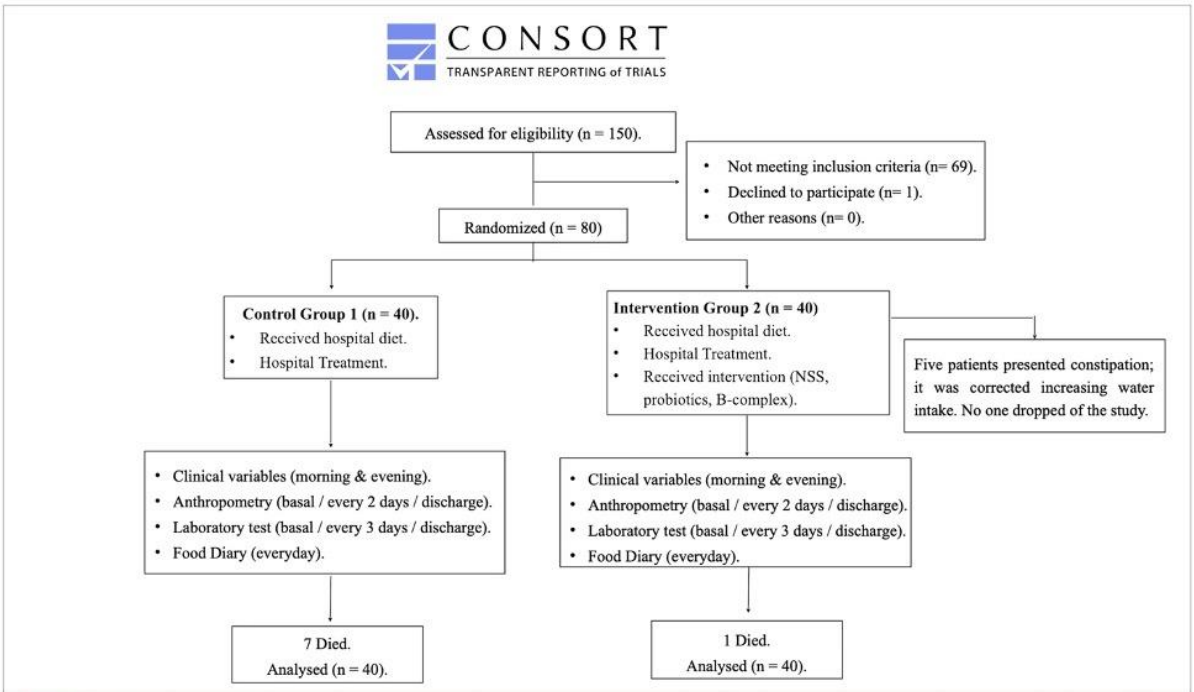

Figure 1. Consort, transparent reporting of trials.

Table 1-A. Clinical characteristics and demographic analysis.

Characteristics	CG Mean (SD / %) n=40	IG Mean (SD / %) n=40	P- value
Median age – years.	53.9 ± 10.3	51.5 ± 11.4	0.351
Female gender – no. (%)	13 (32.5%)	15 (37.5%)	0.407
Male gender – no. (%)	27 (67.5%)	25 (62.5%)	0.407
Risk factors and coexisting conditions – (%)			
Overweight	38 (95%)	36 (90%)	0.338
Obesity	14 (35%)	13 (32.5%)	1
DM 2	13 ± 0.325	11 ± 0.275	0.404
Cardiovascular disease	17 (42.5%)	10 (25%)	0.078
Hyperlipidemia	11 (27.5%)	7 (17.5%)	0.422
Gastrointestinal Disease	14 (35%)	13 (32.5%)	1
Total Risk Factors	2.92 ± 1.42	2.57 ± 1.35	0.261
Covid-19 Symptoms			
Dyspnea	24 (60%)	26 (65%)	0.409
Nausea and vomit	6 (15%)	7 (17.5%)	0.5
Hyposmia	12 (30%)	15 (37.5%)	0.637
Dysgeusia	18 (45%)	20 (50%)	0.412
Headache	26 (65%)	29 (72.5%)	0.315
Myalgia	32 (80%)	30 (75%)	0.395
Diarrhea	18 (45%)	12 (30%)	0.124
Anorexia	20 (50%)	21 (52.5%)	0.500
Total of symptoms	7.05 ± 2.11	6.8 ± 2.23	0.608
Gastrointestinal Clinic			
Bristol	9 (50%)	5 (27.8%)	0.153
Number of defecations	0.54 ± 0.6	0.52 ± 0.73	0.717
Abdominal distension	28 (70%)	28 (70%)	0.596
Vital Signs			
Breathing Frequency - bpm	21.18 ± 3.01	21.48 ± 3.01	0.378
Oxygen Saturation - %	92.73 ± 4.17	94 ± 3.18	0.144
Heart Rate - bpm	70.7 ± 15.4	75.5 ± 9.88	0.105
Temperature – °C	36.27 ± 0.73	36.3 ± 0.62	0.935
Oxygen flow – L/min	5.9 ± 3.82	6 ± 3.29	0.571
qSOFA - pts	0.425 ± 0.59	0.65 ± 0.62	0.100

SD, Standard Deviation. CG, control group. IG, intervention group.

Table 1-B. Clinical characteristics and baseline parameters of CG and IG.

Characteristics	CG Mean (SD / %) n = 40	IG Mean (SD / %) n = 40	P - value
Nutritional Status			
MNA® - pts	11.13 ± 2.26	11.38 ± 1.65	0.828
BMI – kg/m^2	29.35 ± 3.89	29.98 ± 4.07	0.403
Hydric balance – mL/day	-203.4 ± 966	-301.5 ± 1167	0.806
Medication			
Antihypertensive	13 (32.5%)	9 (22.5%)	0.227
Antidiabetics	9 (22.5%)	11 (27.5%)	0.398
Antilipids	3 (7.5%)	3 (7.50%)	0.662
Antibiotics	1 (2.50%)	4 (10%)	0.359
Antiacids	6 (15%)	6 (15%)	0.662
NSAIDs	8 (20%)	12 (30%)	0.220
Laboratory studies			
Hb – g/dL	15.53 ± 2.222	15.54 ± 2.088	0.987
MCHC – g/dL	33.39 ± 1.4	33.46 ± 1.17	0.753
Platelets – 10^3/μL	222.2 ± 53.93	248.4 ± 139.9	0.790
Leukocytes - 10^3/μL	8.97 ± 4.15	8.46 ± 4.36	0.400
Neutrophils - %	83.5 ± 8.87	80.78 ± 9.29	0.172
Glycemia – mg/dL	135.4 ± 59.39	134.8 ± 58.83	0.872
Total cholesterol – mg/dL	142.8 ± 42.82	135 ± 23.53	0.335
Triglycerides – mg/dL	147.5 ± 58.92	132.8 ± 37.39	0.533
AST – U/L	48.06 ± 28.81	46.4 ± 49.65	0.214
ALT – U/L	47.69 ± 31.9	50.44 ± 50.88	0.914
Albumin – g/dL	3.53 ± 0.44	3.57 ± 0.41	0.768
Ferritin – ng/mL	1070 ± 899.3	1270 ± 1142	0.572
Fibrinogen – mg/dL	592.2 ± 170.4	607.4 ± 162.9	0.721
CRP – mg/dL	157.3 ± 106.7	135.3 ± 94.92	0.313
D dimer – ng/mL	291.2 ± 179.9	444.9 ± 954.9	0.927
Creatinine – mg/dL	0.88 ± 0.31	0.86 ± 0.22	0.734
Urea – mg/dL	33.95 ± 15.84	32.95 ± 10.78	0.710
BUN – mg/dL	15.87 ± 7.39	15.43 ± 5.02	0.690
GFR – mL/min/1.73 m^2	90.15 ± 20.2	93.59 ± 17.4	0.673
Procalcitonin – ng/mL	0.364 ± 0.6	0.18 ± 0.188	0.356

The comparison of both groups in the baseline did not show a significant difference in any item analyzed in this study.
SD, Standard Deviation. CG, control group. IG, intervention group. MNA, Mini Nutritional Assessment.

Figure 2. **Kaplan-Meier general survival curve from CG and IG patients**

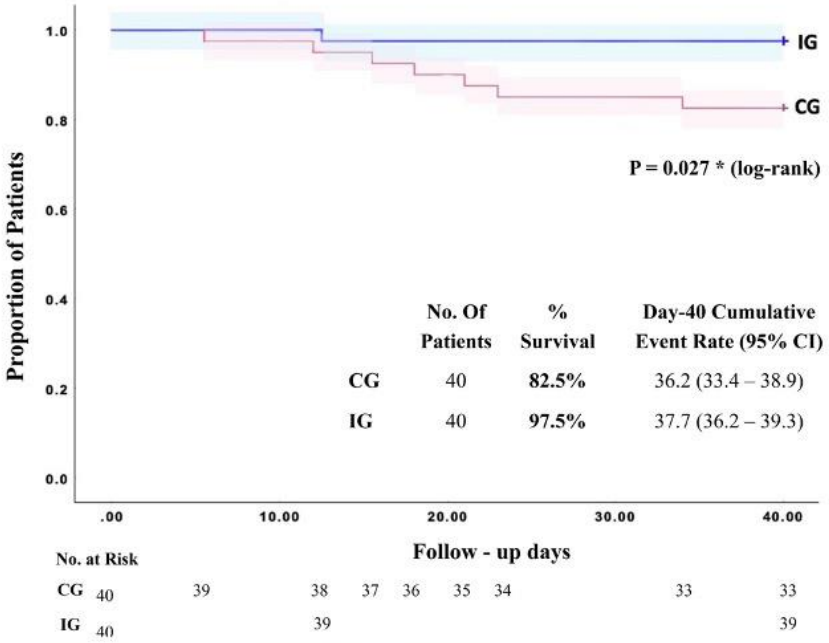

Figure 2. **Kaplan-Meier general survival curve from CG and IG patients.**

The proportion of patients in the IG (blue line) and the CG (red line) included in the study and completed a 40-day follow-up from September 2020 to April 2021. The cumulative proportion of surviving patients was estimated with the Kaplan-Meier method and compared in both groups, from the CG died seven of 40 patients (surveillance 82.5%, mean 36.22, 95% of confidence interval [CI] 33.46 to 38.98), otherwise from de IG died one of 40 patients (surveillance 97.5%, mean 39.31%, 95% of [CI], 37.98 to 40.64). This showed a significant difference of IG compared to CG * $p=0.027$ (Log Rank test, 95% of [CI]).

Figure 3. **Kaplan-Meier survival curve from patients Receiving Mechanical Ventilation of the CG and IG.**

Figure 3-A

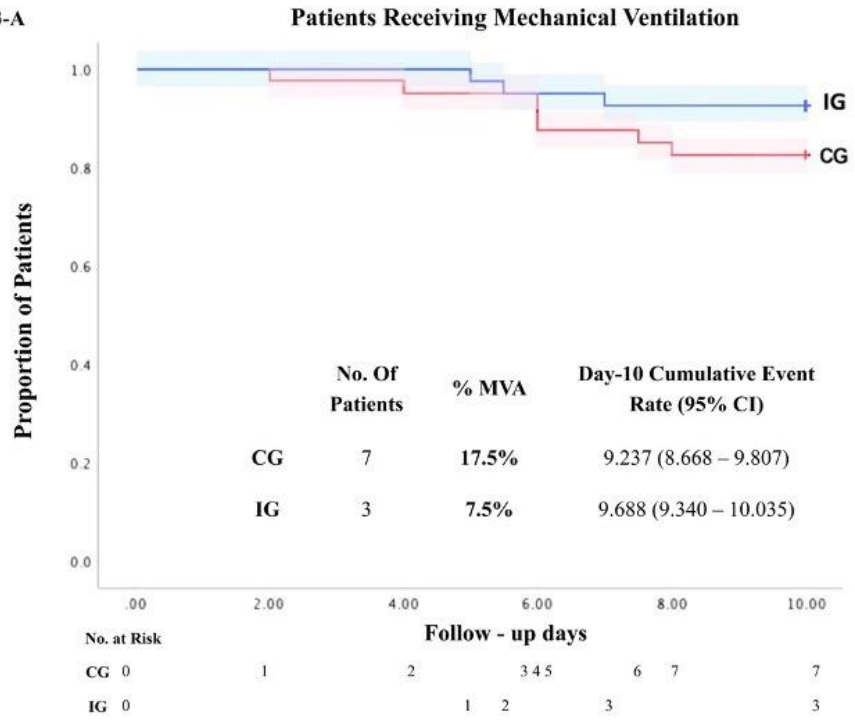

Figure 3-B

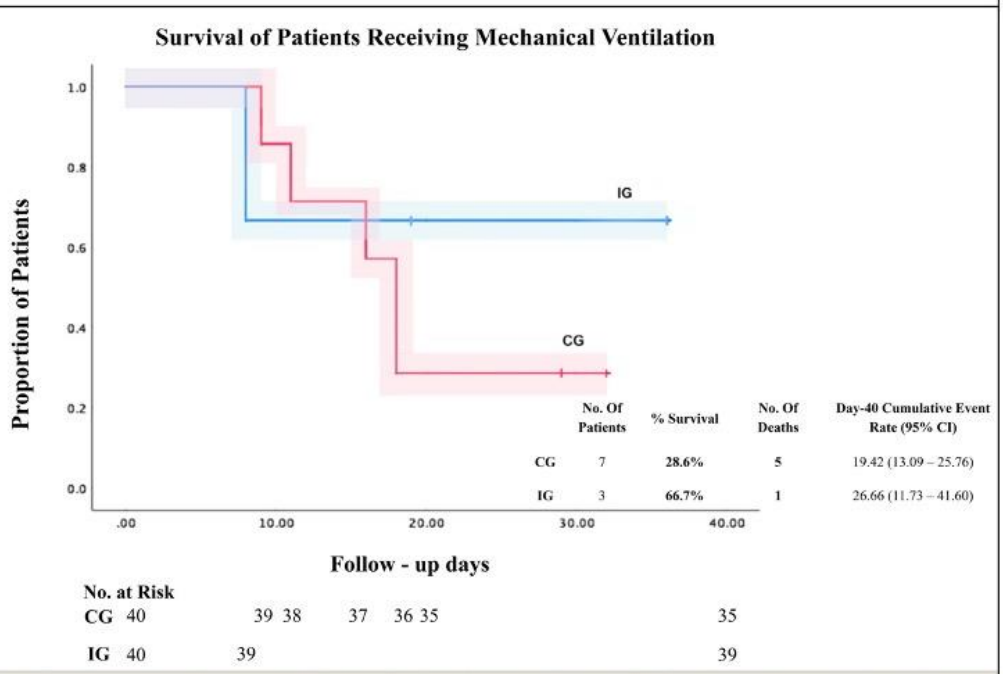

Figure 3. **Kaplan-Meier survival curve from patients Receiving Mechanical Ventilation of the CG and IG.**

The proportion of patients with MVA from CG and the IG were included in the study and completed 40-day follow-up from September 2020 to April 2021. **(Figure 3-A)** IG and CG were analyzed with the Kaplan-Meier method comparing both groups to MVA progression, from CG seven patients progressed to MVA (17.5%, mean 9.68%, [IC] of 95%, 8.66 to 9.80); meanwhile, from IG three patients progressed to MVA (7.5%, mean 9.68%, [IC] of 95%, 9.34 to 10.03), this represents a 10% decrease in MVA progression of IG in comparison with CG. **(Figure 3-B)** In overall survival and mortality with MVA, five out of seven patients died in CG (71.4%, mean 19.42, [CI] of 95%, 13.09 to 25.76). One out of three patients died in IG (33.5%, mean 26.66, [IC] of 95% 11.73 to 41.6), this represents the 38.1% decrease in mortality with MVA in IG compared to CG.

Table 2-A. Clinical evolution and 40-day follow up.

	CG				IG				Intergroup p-value
Clinical Evolution	**n**	**Baseline**	**Day 3**	**P value**	**n**	**Baseline**	**Day 3**	**P value**	
Oxygen flow - L (intragroup)	40	5.9 ± 3.8	6 ± 4.4	0.919	40	6 ± 3.2	4.5 ± 3.5	0.014 *	
qSOFA - pts	40	0.42 ± 0.59	0.51 ± 0.57	0.608	40	0.65 ± 0.62	0.43 ± 0.49	0.040 *	
Number of defecations on day 3	37		0.81 ± 0.90		36		1.41 ± 1.13		0.014 *
Distension on day 3	31		51.60%		31		19.40%		0.008 *
PHQ-9 test – pts (intragroup)	6	3.66 ± 2.5	1.50 ± 2.8	0.187	10	5.3 ± 3.4	1.9 ± 1.4	0.003 *	
Oxygen Saturation >90% on day 3 -%	40		85%		40		92.50%		0.241
Hydric Balance on day 3 - mL	17		123.4 ± 453.8		18		456.6 ± 485.5		0.043 *
Bristol scale on day 3 - %	24		33.30%		31		41.90%		0.356
40-day follow-up			**Day 40**				**Day 40**		
Saturation without Supplementary Oxygen - %	28		90.39 ± 3.4		38		92.08 ± 2.5		0.030 *
Need for home Oxygen flow - %	27		85.2%		39		66.70%		0.078
Time of home Oxygen use – days	17		57.6 ± 24.6		23		43.8 ± 16.2		0.098
Post-covid syndrome - %	24		37.50%		34		23.50%		0.195
Weight decrease - % of patients	11		72.70%		18		44.40%		0.135
Gastrointestinal symptoms - %	24		16.70%		37		8.10%		0.266

Table 2-A The following table shows the results of the intergroup analysis between the IG (Intervention Group) and the CG (Control Group) for different parameters in the baseline or with a complete 40-day follow-up. Deceased patients were excluded. * *p-value* <0.05.

Table 2-B. Association of baseline laboratory parameters and general mortality.

	Discharge (n=72)		Death (n=8)		
Baseline values	**n**	**%**	**n**	**%**	**P value**
Fribrinogen >700 mg/dL	13	18.50	6	75.00	**0.002 ***
Procalcitonin >0.5 ng/mL	4	5.5	4	50	**0.003 ***
Blood Urea Nitrogen >22 mg/dL	5	6.90	4	50	**0.004 ***
RCP >150 mg/L	28	38.8	7	87.5	**0.011 ***
Neutrophils >80%	45	62.50	8	100	**0.031 ***
Leucocytes >10 10^3/µL	18	25.00	5	62.50	**0.040 ***
Urea >40 mg/dL	12	16.6	4	50	**0.047 ***

Table 2-B. The results show the association between laboratory parameters taken in the baseline, with the overall mortality. Analysis was performed with Fisher's exact test. * p-value < 0.05.