Title

Effectiveness and tolerance of enteral nutrition in critically ill patients with COVID-19

Comparative efficacy and tolerability of enteral nutrition in critically ill patients with COVID-19: A Cohort Study.

Running title

Effectiveness enteral nutrition in COVID-19

COVID-19 efficacy of enteral nutrition

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SARS-CoV-2, COVID-19, enteral nutrition, nutrients, prone ventilation, diarrhea

List of abbreviations

WHO	World Health Organization
ARDS	Acute respiratory distress syndrome
EN	Enteral nutrition
ICU	Intensive care unit
ESPEN	European Society for Clinical Nutrition and Metabolism
ASPEN	American Society for Enteral and Parenteral Nutrition
AUSPEN	Australian Society for Enteral and Parenteral Nutrition
PN	Parenteral nutrition
SOFA	Sequential Organ Failure Assessment
APACHE	Acute Physiology and Chronic Health Evaluation
BMI	Body mass index
mNUTRIC	Modified nutrition risk in the critically ill
IMM	Immunomodulatory
ω3	ω3 fatty acids
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
MD	Maltodextrins
SD	Standard deviation
IQR	Interquartile range

Abstract

This study compared the efficacy and tolerability of three enteral formulas in critically ill patients with COVID-19 who were ventilated and prone position. Enteral formulas: a) immunomodulatory (IMM), b) ω3 (ω3) and c) maltodextrins (MD). Primary outcome was percentage of patients who received both 80% of their protein and calorie targets at 3 days after enrolment. Secondary, mechanical ventilation-free time (MVF), ICU mortality, and markers of nutritional status. Tolerance of enteral nutrition (EN) was evaluated by diarrhea and gastroparesis rate. 231 patients were included, primary outcome achieved was in ω3 group (76.5% vs 59.7% and 35.2%, $p < 0.001$) vs IMM and MD groups. MVF were longer in ω3 and MD groups 23.11 ± 34.2 hours and 22.59 ± 42.2 hours vs IMM group 7.9 ± 22.6 hours ($p < 0.01$). Prealbumin final was 20.3 ± 10.8 mg/dL and 20.3 ± 9.5 mg/dL in IMM and ω3 groups vs 16.4 ± 7.0 mg/dL ($p < 0.01$) MD group. Transferrin were 151.5 ± 53.6 mg/dL and 152.1 ± 50.0 mg/dL in IMM and ω3 groups vs 133.7 ± 48.3 mg/dL ($p < 0.05$) MD group. Increase of lymphocytes was greater in ω3 1056.7 ± 660.8 cells/mm3 vs 853.3 ± 435.9 cells/mm3 and 942.7 ± 675.4 cells/mm3 ($p < 0.001$) IMM and MD groups. Diarrhea and gastroparesis occurred in 5.1% and 3.4% respectively. The findings of this study indicate that EN is a safe and well-tolerated intervention. The ω3 formula compared to IMM and MD did improve protein and calorie targets.

Introduction

The global pandemic caused by the SARS-CoV-2 virus first emerged in Wuhan, China, in late 2019. Subsequently, the World Health Organization (WHO) has declare the end of global health emergency, noting that the disease will continue to affect the global population. In recent weeks, there has been a notable increase in the prevalence of the JN.1 variant globally [1]. It has been observed that older adults and patients with comorbidities such as diabetes mellitus, hypertension, and obesity have been the most vulnerable to severe SARS-CoV-2 infection [1,2]. Patients with severe COVID-19 exhibit a prominent systemic inflammatory response, characterized by the release of pro-inflammatory cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor-α. This cytokine storm induces a severe metabolic alteration, increasing both resting energy expenditure and protein catabolism [3]. Acute respiratory distress syndrome (ARDS) following SARS-CoV-2 pneumonia represents the most severe form of pulmonary compromise and, like that produced by other causes, also leads to an increase in energy expenditure and protein catabolism [4].

The initiation of early enteral nutrition (EN) within 48 hours of admission to the intensive care unit (ICU) in hemodynamically stable patients is considered the best practice for the prevention of nutritional and metabolic deterioration [5,6]. Adequate calorie and protein intake have been linked with enhanced outcomes and a reduction in the number of days spent on mechanical ventilation among critically ill patients. On the other hand, the accumulation of caloric deficits and negative protein balances have been linked with an increased incidence of complications, particularly healthcare-associated infections, a longer hospital stay, and a higher in-hospital mortality rate [7-9]. Although Indirect calorimetry remains the gold standard to assess energy expenditure, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends its use as long as ensured sterility of the measurement system [10]. Other societies, such as the American Society for Enteral and Parenteral Nutrition (ASPEN) and the Australian Society for Enteral and Parenteral Nutrition (AUSPEN), report that indirect calorimetry could increase the risk of infection in healthcare workers [11,12]. In addition to a reduction in the number of medical staff and a high level of patient demand, the use of this method was also limited. ESPEN recommends a contribution of 20 kcal/kg/day during the acute phase and a progressive increase to 80-100% of energy requirements and a protein goal of 1.3 g/kg/day [10]. In contrast, ASPEN

recommends a protein intake of 1.2 – 2.0 g/kg/day and 15-20 kcal/kg/day in critically ill patients with COVID-19 [11].

The type of enteral formula and the optimal amount of nutrition administered is controversial in patients with ARDS and significant differences in nutritional treatment have been noted [5,6,13]. The recommendation based on expert consensus, to use a standard polymeric formula when starting EN. However, immunomodulatory enteral formulations in some meta-analyses have suggested benefit effects in reducing infection, hospital stay, and duration of mechanical ventilation [10]. In the case of ARDS caused by SARS-CoV-2, being a new viral disease, there is a lack of information on nutritional support practices and on the characteristics and benefits of different feeding formulas, a situation that needs to be improved, as SARS -CoV-2 infection continues to impact healthcare resources worldwide. Furthermore, the prone position has been widely utilised in patients with severe hypoxemia, including those with ARDS caused by SARS-CoV-2. However, the evidence regarding the safety of this approach and the potential increased risk of feeding intolerance remains inconclusive [14]. We hypothesized that an enteral feeding formula immunomodulatory in COVID-19 patients ventilated in ICU and prone position would be associated with achieving an optimal amount defined as 80% of the 24-hour of protein and calorie target. Therefore, this study aimed to provide an overview the mode of nutrition therapy by comparing the fulfilment of caloric and protein targets; additionally, a secondary aim was to determine if any formula enteral may impact in mechanical ventilation-free time, mortality and markers of nutritional status.

Methods

Study design and population.

A prospective cohort study was conducted on consecutive adult patients with severe SARS-CoV-2 infection admitted to the multidisciplinary intensive care unit of a third referral hospital in Mexico City between March 2020 and March 2022. All patients with SARS-CoV-2 requiring invasive mechanical ventilation with an expected duration >72 h in the prone position and receiving enteral nutrition within the first 48 h after admission were included. The patients were diagnosed with SARS-CoV-2 pneumonia according to the WHO criteria, including characteristic symptoms of ARDS: dyspnea, tachypnea, decreased oxygen saturation, with oxygen requirement of 6 L/min, and detection of SARS-CoV-2 virus by real-time reverse transcription polymerase chain reaction assays. Patients requiring exclusive parenteral nutrition (PN), those receiving PN

for less than 72 h, those who died within 24 h of ICU admission and those diagnosed with chronic kidney disease KDIGO IV-V were excluded (**Figure 1**). The required sample size was calculated using a 95% confidence level and a margin of error of 4%, based on the annual admissions to the ICU in the previous year. The resulting sample size was 231total subjects, who were consecutively enrolled in the study. The institutional ethics committee at participating center approved the study protocol (Protocol Number 0767/20-1), and the study was conducted in accordance with the Declaration of Helsinki as revised in 2013. Informed consent was waived because we used anonymized retrospective data.

Data collection

Data were obtained from ICU admission and daily follow-up sheets from the nutritional support unit. Data collected included patient demographics and disease severity, anthropometric measurements, laboratory data (markers of nutritional status), mechanical ventilation-free time and ICU mortality.

Demographic variables. The demographic data recorded were sex, age, presence of diabetes mellitus, arterial hypertension, dyslipidemia, hypothyroidism, and chronic lung disease. The Sequential Organ Failure Assessment (SOFA) score and the Acute Physiology and Chronic Health Evaluation (APACHE) II prognostic classification were used to assess the severity of each patient's illness. The PaO2/FiO2 index was calculated and classified according to the Berlin criteria [(15)].

Anthropometric measurements. The measurements included weight (kg), registered by the Stryker InTouch metabolic beds, and height (m). Body mass index (BMI) was calculated, and patients were classified according to the WHO reference ranges [(16)]. Nutritional risk was assessed using the modified nutrition risk in the critically ill (mNUTRIC) score [(17)].

Laboratory tests. The laboratory tests registered were performed on venous blood according to the standardized methods of the hospital's central laboratory and included total leukocyte count (cells/mm3), neutrophils (cells/mm3), prealbumin (mg/dL), transferrin (mg/dL), and albumin (g/dL).

Nutrition prescription

The use of indirect calorimetry was not feasible due to the high risk of contamination by the dispersion of SARS-CoV-2 virus through aerosols. Therefore, caloric requirements were determined according to standard protocols which consist of using the Harris-Benedict equation

and adjust the weight as follows: using current weight for patients with normal BMI (18.5-24.9 kg/m2), ideal weight for those with low BMI (<18.5 kg/m2), and adjusted weight for cases with obesity and overweight (BMI >25 kg/m2). An initial stress factor of 1.3 was added to the resulting value in all cases. The protein requirement was initially established at 1.7 g/kg/day; thereafter, both requirements were subsequently adjusted based on clinical evolution, laboratory test results and nitrogen balance. The decision to prone was made by the intensivist physician based on the severity of ARDS and response to initial treatment; and prone was performed by trained staff according to standard unit protocols. Nutrition prescription was initiated by the clinical nutrition specialist physicians as early as possible (within 24–48 h) in the absence of contraindications based on ESPEN and ASPEN guidelines for nutritional support in critically ill patients.

Nutrition therapy

The feeding at admission, prescription, volume prescribed, volume administered and type enteral formulae were recorded. The three types of enteral formula that were used were as follows: a) IMM: isocaloric, high-protein, immunomodulatory with arginine, glutamine, branched-chain amino acids, ω3 fatty acids, medium-chain triglycerides, and antioxidants. It provides 1 kcal/1 mL, 32.7% protein, 47.6% carbohydrates, and 19.7% lipids (Enterex IMX® Victus Inc.); b) ω3: high-calorie, high-protein, supplemented with ω3 fatty acids, 0.50 g of eicosapentaenoic acid (EPA), and 0.21 g of docosahexaenoic acid (DHA). It provides 1.5 kcal/1 mL, 27% protein, 33% carbohydrates, and 40% lipids (Supportan DKN® Fresenius KABI.); and c) MD: maltodextrins and ω3 and ω6 fatty acids. It provides 0.91 kcal/mL, 20% protein, 46% carbohydrates, and 34% lipids (Glucerna® Abbott.) plus a glutamine module with *Lactobacillus reuteri*, which provides 10 g of L-glutamine and 10^8 CFU of *Lactobacillus reuteri* (Glutapak®R Pisa).

All patients had a nasogastric/orogastric tube inserted and position was always confirmed with a chest X-ray prior to prone positioning. Enteral nutrition was administered by continuous infusion at an initial rate of 20 ml/h, increased then to 40 ml/h and gradually according to the gastric residual volume until the 80% caloric target was reached within the first 72 h. If the gastric residual volume was > 500 ml, the infusion rate was reduced and the EN stopped if necessary. The EN was resumed at an infusion rate of 20 ml/h when the gastric residual volume was ≤ 500 ml. Patients were followed until discharge from the ICU or death. If the patient presented diarrhea the infusion rate was decreased 20-40 ml/h for the next 24 h and if the symptoms

persisted the EN was stopped. In case of gastroparesis, intravenous prokinetics (metoclopramide 10 mg 3 times a day) were prescribed.

Outcomes

The primary outcome was the percentage of patients receiving both 80% of the 24-hour caloric and protein targets at 3 days after enrolment. Secondary outcomes were mechanical ventilation-free time, ICU mortality, and markers of nutritional status (albumin, prealbumin, transferrin and lymphocytes). Tolerance of EN was assessed by the rate of diarrhea and gastroparesis. Gastroparesis was defined as a gastric residual volume > 500 ml, and diarrhea as more than three watery stools per day for two consecutive days. Nutritional impact was evaluated by the variation of albumin, prealbumin and transferrin measured at baseline and after enrolment.

Statistical analysis.

Baseline characteristics of the groups were analyzed using descriptive statistics. Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR, 25th and 75th percentiles). Categorical data are expressed as frequencies and percentages. Comparisons between groups were made using the Chi-square or Kruskal-Wallis test for qualitative variables, as appropriate and the Student t test for quantitative variables. Differences between repeated measurements in each group were analyzed using by repeated-ANOVA. A significance level of 5% was used for all statistical tests. Data were analyzed using SPSS statistical software for Windows (version 21.00, SPSS Inc).

Results

A total of 231 patients were included during the study. The demographic characteristics, anthropometric measurements, and assessment scales performed on admission to the ICU are shown in **Table 1**.

Enteral nutrition was started during the first 24 h after admission to the ICU. The mean calories prescribed were 22.5 ± 3.3 kcal/kg/day (95% CI, 22.1 – 22.9) and the mean protein prescribed were 1.7 ± 0.3 g/kg/day (95% CI, 1.5 – 1.6). A total of 7.7% (n = 18) patients received PN during their stay in addition to enteral nutrition. The decision to combine them was mostly based on the presence of digestive tract bleeding, frequent in IMM group compared to the ω3 and MD groups ($p < 0.05$). Patients in the ω3 group showed low levels of gastric residue compared to the other two groups ($p = 0.001$). The characteristics of the EN contributions are shown in **Table 2**.

Nutrition provision

Primary outcome

The percentage of patients achieving the primary outcome was significantly higher in the ω3 group (76.5% vs 59.7% and 35.2%, $p < 0.001$) compared to the IMM and MD groups respectively. Patients achieved a mean of 92.9% (SD 16.6%; 95% CI, 90.7% - 95.0%) of the caloric target during the first 72 h with statistically significant differences between groups, with the ω3 group achieving the highest value ($p < 0.001$). Participants achieved a mean of 88.4% (SD 18.3%; 95% CI, 86.3% - 90.2%) of protein target (g/day) with significant differences between groups; with IMM having the highest value ($p = 0.001$) **(Table 2).**

Secondary Outcomes.

Mechanical ventilation-free time was significantly longer in the ω3 and MD groups 23.11 ± 34.2 hours (95% CI 15.5-30.68) and 22.59 ± 42.2 hours (95% CI 12.36-32.82) respectively compared to the IMM group 7.9 ± 22.6 hours (95% CI 2.93-12.88) ($p < 0.01$) (**Figure 2**). The ICU mortality were similar in the three groups (53.6 vs 59.2, 69.1%, $p = 0.153$).

Regarding markers of nutritional status and compared to baseline values, the IMM group showed statistically significant increase in lymphocytes at the end of follow-up, the ω3 group showed differences in lymphocytes, prealbumin and transferrin levels, and the MD group also in lymphocytes (all $p < 0.05$) **(Table 3).** Specifically, the mean final prealbumin observed was 20.3 ± 10.8 mg/dL and 20.3 ± 9.5 mg/dL in the IMM and ω3 groups compared with 16.4 ± 7.0 mg/dL ($p < 0.01$) in the MD group. In the case of transferrin, the mean final values were 151.5 ± 53.6 mg/dL and 152.1 ± 50.0 mg/dL in the IMM and ω3 groups compared with 133.7 ± 48.3 mg/dL ($p < 0.05$) in the MD group was calculated. The increase of lymphocytes was particularly remarkable in the ω3 group 1056.7 ± 660.8 cells/mm3 compared with 853.3 ± 435.9 cells/mm3 and 942.7 ± 675.4 cells/mm3 ($p < 0.001$) in the IMM and MD groups. Although all three groups showed a change in markers of nutritional status levels, the deltas of change by groups are shown in **Table 3.**

Gastrointestinal complications and tolerance

Gastrointestinal complications were observed in 12.5% of participants. The most frequent was diarrhea and gastrointestinal bleeding in 5.1% (n=12) of both cases, which led to a reduction in the infusion rate of EN or temporary suspension (**Table 4)**. Eighteen patients required total PN, with a median duration of 7.6 ± 4.6 days. Statistically significant differences were observed in the tolerance of enteral nutrition. The percentage of diarrhea observed was lower in the ω3 group

1.2% compared to 4.8% and 10.2% (p = 0.003) in the IMM and MD groups, respectively. Gastroparesis occurred in 4.8% and 1.2% (p = 0.003) in the IMM and ω3 groups, respectively, compared to the MD group (p = 0.001).

Discussion

Adequate nutritional support for critically ill patients with SARS-Cov-2 infection was challenging for several reasons, especially during the early stages of the pandemic. According to the results of our study, patients admitted to the ICU had important risk factors, 87.9% of them were overweight or had some degree of obesity, and more than 30% had chronic diseases such as hypertension and diabetes. These comorbidities re associated with poorer disease prognosis of the disease and have been linked to a significant deterioration in nutritional status during hospitalization, despite admission with low nutritional risk according to the mNUTRIC score [2,18].

The recommendations given so far for the nutritional support of critically ill patients with SARS-CoV-2 infection suggest the use of high-protein, and iso-osmolar polymeric formulas are safe and well tolerated [19,20]. There really are no unified recommendations regarding to use formulas with components that have shown certain benefits in other diseases, as is the case of formulas supplemented with ω3 fatty acids or formulas known as immunomodulators. However, the results of this study show that the use of enteral formulas supplemented with ω3 fatty acids, which have the characteristic a higher energy density and high protein, facilitates achieving the caloric and protein requirements of patients. In a study by Doaei et al [21], the addition of 0.4 g of EPA and 0.2 g of DHA to an enteral formula was associated with better renal and respiratory function and longer survival compared to critically ill control patients with COVID-19. On the other hand, a recent systematic review by Mazidimoradi et al [22] concluded that ω3 fatty acid deficiency is associated with greater mortality and severity of disease in critically ill patients with COVID-19. In our results we do observe benefits of the formula supplemented with ω3 fatty acids compared to other formulas in providing 80% of the caloric and protein requirements. In addition, we observed that the mechanical ventilation-free time was significantly longer. Secondarily, this formula was associated with improvement in some markers of nutritional status. This effect may have been due to it was a high-calorie and high-protein formula that facilitated meeting the requirements of patients with lower volume and better tolerance during prone position.

As for the immunomodulatory formula, higher levels of lymphocytes were recorded compared to the other groups. However, these values were lower than the change observed in the group supplemented with ω3. The evidence of the effect of immunomodulatory formulas in critically ill patients with COVID 19 is much more limited, and studies have found few benefits when using this type of formula, as demonstrated by the clinical trial of Pimentel et al [23], which reported a decrease in the levels of C-reactive protein in patients receiving an immunomodulatory formula, with no significant effect on any other variable. In a pilot study of Scarcella et, observed that immune-nutrition prevented malnutrition development with a significant decrease of inflammatory markers in overweight patients admitted to the semi-intensive CODIV-19 [24].

In the group that received the formula with maltodextrins plus glutamine we observed lower intake of calories and proteins compared to other groups. As for the secondary outcomes a significant longer ventilator-free time was observed, similar to the supplemented with the ω3 group. Lower levels of prealbumin, albumin, and transferrin were found to the end of follow-up compared with the other groups. This may be related to the fact that this formula contained a lower protein amount despite being added with a protein module it is thus more complex to reach the energy and protein requirements.

Early initiation of enteral nutrition is recommended because of the reduced length of ICU stay, time on mechanical ventilation and the presence of complications [6,19,25]. However, as shown by Farina et al [26], the evidence for this benefit in critically ill patients with COVID-19 is inconclusive. In our study, all patients started EN within the first 24 h of ICU admission, eight out of ten patients met their energy requirements within the first 72 h, and seven out of ten patients met their protein requirements within the same period. This study found an association between these variables and a reduction in mechanical ventilation-free time.

Despite the early initiation of EN in our study, the infusion rate was frequently reduced due to the presence of gastrointestinal complications, deterioration of the patient's general condition, or the use of prone positioning. In a systematic review by Bruni et al [27], they concluded that patients in the prone position showed a higher incidence of EN discontinuation and vomiting episodes, but without changes in MV time, length of stay, or mortality compared to patients in the supine position. On the other hand, Ellis et al [28] concluded in a review that the use of EN in the prone position is comparable to that in the supine position, without a greater risk of complications, and safe in ventilated patients with COVID-19. In our experience, we agree with

Behrens et al [29] who propose that the use of EN should not be contraindicated in patients in the prone position, nor should it affect the infusion rate or be an indication for the use of PN. Therefore, we suggest that the knowledge of the different members of the health care team regarding the safety of EN administration in the prone position should be strengthened, in order to avoid modifying or suspending the intervention, which could be detrimental to the patient's clinical condition, due to non-compliance with the established caloric and protein targets.

Finally, gastrointestinal complications represent a significant challenge in the context of daily medical practice, with the potential to impact compliance with nutritional targets in patients diagnosed with COVID-19. A higher prevalence of diarrhea was observed in the MD group (5.1% vs. 3.6%), which may be attributed to the increased fibre content of these enteral formulas. This may also have contributed to the difficulty in achieving the set goals. In cases of an increased number of complications, enteral nutrition is reduced or initiated to parenteral nutrition. The low incidence of complications lends support to the observation that enteral nutrition in critically ill patients with SARS-CoV-2 infection is well tolerated, has a low incidence of associated complications, and represents an excellent strategy to ensure nutritional support for patients with this pathology in the ICU.

This study has some limitations. Frist, our study was conducted during the initial waves of the SARS-CoV-2 pandemic, a period during which there was a lack of experience in managing the disease Second, the published data are derived from a single referral hospital center, which may introduce selection biases, given that outside the hospital unit there is limited access to the enteral formulas. Third, our unit has a standardized protocol for the initiation and progression of infusion enteral nutrition, and it is uncertain that the same results would be observed using a different protocol. Fourth, the percentage of diarrhea and gastroparesis reported can be different to that reported in other studies, this could be explained by the heterogeneity in the definition of diarrhea and gastroparesis.

Conclusions

In conclusion, the present study demonstrated a positive effect when using a high-calorie, high-protein formula with ω3 fatty acids to achieve calorie and protein targets. Secondly, a reduction in mechanical ventilation-free time was observed, which was associated with a lower deterioration of albumin levels and improved levels of lymphocytes, prealbumin and transferrin. Finally, we consider that those patients with critical illness due to SARS-CoV-2 should receive

formulas that ensure an adequate supply of energy and nutrients, in accordance with international recommendations. It is therefore essential to consider the characteristics of the population in question when selecting an appropriate formula.

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Author Contributions. The authors confirm their contribution to the articles as follows: study conception and design P.C.E.; data collection O.G.S, C.G.J.A, L.C.Y..; statistical analysis P.C.E., O.G.S.; analysis and interpretation of results P.C.E., O.G.S., C.G.J.A, G.L.J.; draft article preparation P.C.E, O.G.S, C.G.J.A, G.L.J.,L.C.Y. All authors reviewed the results, edited, and approved the final version of the article.

Data Availability Statement. The data supporting the findings of this study are available on reasonable request from the corresponding authors.

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Table 1. Clinical characteristics according to different enteral formulae

Characteristics	Total n = 231	IMM group n = 82	ω3 group n = 81	MD group n = 68
Age (years)	54.5 ± 12.6	53.0 ± 12.8	52.9 ± 13.6	58.3 ± 11.1*
Sex (n, %)	80, 34.6	26, 31.7	25, 30.9	29, 42.6
Women	80 (34.6)	26 (31.7)	25 (30.9)	29 (42.6)
Men	151 (65.4)	56 (68.3)	56 (69.1)	39 (57.4)
Weight (kg)	84 ± 17.3	85.5 ± 18.2	89.8 ± 16.9	75.3 ± 12.6*
BMI (kg/m^2)	30.7 ± 5.8	31.2 ± 5.9	31.7 ± 6.1	28.7 ± 4.8*
NUTRIC score	3.5 ± 1.5	3.4 ± 1.7	3.5 ± 1.3	3.7 ± 1.2
SOFA	9.0 ± 2.8	9.4 ± 3.9	8.8 ± 2.0	9.0 ± 2.1
APACHE II	18.6 ± 5.5	18.5 ± 7.0	19.2 ± 4.5	17.9 ± 4.4
PAFI	103.7 ± 45.2	117.8 ± 62.7	93.5 ± 22.5	98.9 ± 35.4
Pre-existing conditions (n, %)				
Overweight/Obesity	200 (86.6)	71 (86.6)	75 (92.5)	54 (79.4)
Hypertension	77 (33.3)	32 (39.0)	26 (32.0)	35 (51.4)
Type 2 Diabetes	84 (36.3)	23 (28.0)	26 (32.0)	35 (51.4)
Hypothyroidism	8 (3.4)	2 (2.4)	5 (6.1)	1 (1.5)
COPD	2 (0.8)	1 (1.2)	1 (1.2)	0

IMM: immune-modulating enteral formula. ω3: enteral formula with ω3 fatty acids. MD: maltodextrin + glutamine. BMI: Body mass index. NUTRIC Score: Nutrition Risk in the Critically Ill. SOFA: Sequential Organ Failure Assessment. APACHE II: Acute Physiology and Chronic Health Evaluation. PAFI: index PaO2/FiO2. Data shown as percentage, mean ± standard deviation and median.

* $p < 0.05$

Table 2. Characteristics and Tolerance of Enteral Nutrition.

Characteristics	Total n = 231	IMM group n = 82	ω3 group n = 81	MD group n = 68	p
Started enteral nutrition within 24h, n (%)	231 (100)	82 (100)	81 (100)	68 (100)	0.191
Calories prescribed kcal/kg/day	22.5 ± 3.3	22.5 ± 3.5	22.2 ± 3.0	23.0 ± 2.2	0.283
Protein prescribed g/kg/day	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.2	0.210
Percent goal kcal day 3	92.9 ± 16.6	81.9 ± 23.3	99.5 ± 3.6	98.1 ± 7.1	0.001*
Percent goal protein day 3	88.4 ± 18.3	98.5 ± 17.7	90.3 ± 12.4	73.9 ± 15.4	0.001*
≥80% of Total caloric target day3, n (%)	200 (86.5)	54 (65.8)	80 (98.7)	66 (97)	0.001*
≥80% of Total protein target day3, n (%)	157 (67.9)	69 (84.1)	63 (77.7)	25 (36.7)	0.001*
≥80% Total caloric and protein target day 3, n (%)	135 (58.4)	49 (59.7)	62 (76.5)	24 (35.2)	0.001*
High gastric residual volume	513.8 ± 341.2	527.1 ± 343.4	395.8 ± 304.1†	638.4 ± 337.5	0.001†
Received parenteral nutrition, n (%)	18 (7.7)	9 (10.9) #	0	9 (13.2) #	0.01#

IMM: immune-modulating enteral formula. ω3: enteral formula with ω3 fatty acids. MD: maltodextrin + glutamine. Data shown as percentage, mean ± standard deviation and median.
* all $p < 0.001$, † $p < 0.001$ compared with IMM and MD, # $p < 0.01$ compared with ω3,

Table 3. Laboratory tests. Measurement of markers of nutritional status during follow-up

Characteristics	IMM group n = 82			ω3 group n = 81			MD group n = 68		
	BASELINE	FINAL	Δ	BASELINE	FINAL	Δ	BASELINE	FINAL	Δ
Lymphocytes (cells/mm3)	831.1 ± 784.5	853 ± 435.9*	22.8	645.9 ± 367.8	1056.7 ± 660.8*†††#	410.8	610.5 ± 378.5	942.7 ± 675.4*	332.2
Albumin (mg/dL)	2.9 ± 0.4	2.6 ± 0.4*††	0.3	3.0 ± 0.3	2.7 ± 0.5*††	0.3	3.0 ± 0.43	2.6 ± 0.5*	0.4
Prealbumin (mg/dL)	21.6 ± 11.0	20.3 ± 10.8*	1.3	19.5 ± 9.7	20.3 ± 9.5*	0.8	17.1 ± 7.1	16.4 ± 7.0*	0.7
Transferrin(mg/dL)	164.3 ± 5	151.5 ± 53.6*†	12.8	150.1 ± 38.9	152.1 ± 50.0*†	2.0	151.9 ± 48.5	133.7 ± 48.3*	18.2

IMM: immune-modulating enteral formula. ω3: enteral formula with ω3 fatty acids. MD: maltodextrin + glutamine. Data shown as percentage and median. Δ change (delta) scores.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, # $p < 0.001$ compared with IMM, † $p < 0.05$ compared with MD, †† $p < 0.01$ compared with MD, ††† $p < 0.001$

Table 4. Gastrointestinal Complications

Characteristics	Total n = 231	IMM group n=82	ω3 group n = 82	MD group n = 68
General complications, n (%)	29(12.5)	17 (20.7)	3 (3.6) *	9 (13.2)
GIB, n (%)	12 (5.1)	9 (10.9)	1 (1.2)	2 (2.9)
Diarrhea, n (%)	12 (5.1)	4 (4.8)	1(1.2)	7 (10.2)
Gastroparesis n (%)	8 (3.4)	4 (4.8)	1 (1.2)	0

IMM: immune-modulating enteral formula. ω3: enteral formula with ω3 fatty acids. MD: maltodextrin + glutamine. GIB: Gastrointestinal Bleeding.

* $p < 0.05$ compared with IMM and MD

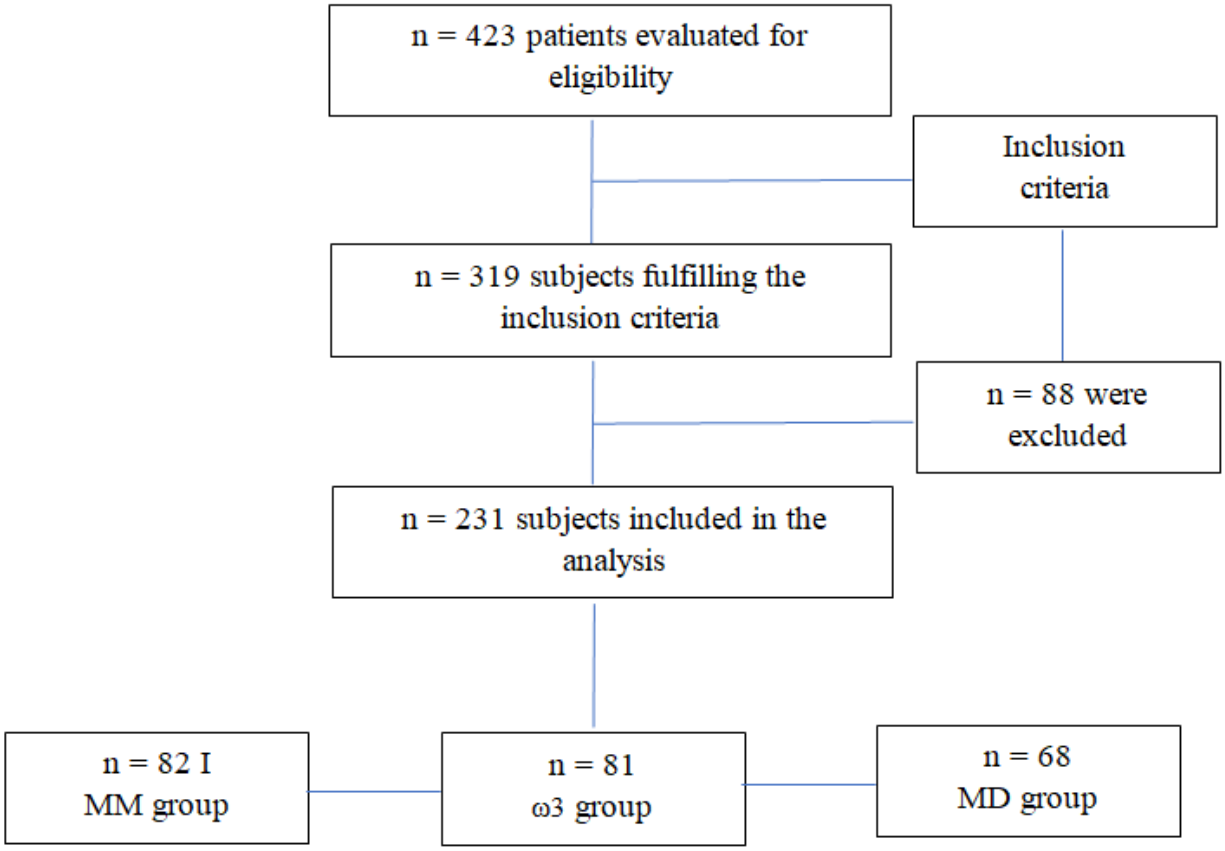

Figure 1. The flowchart of recruitment

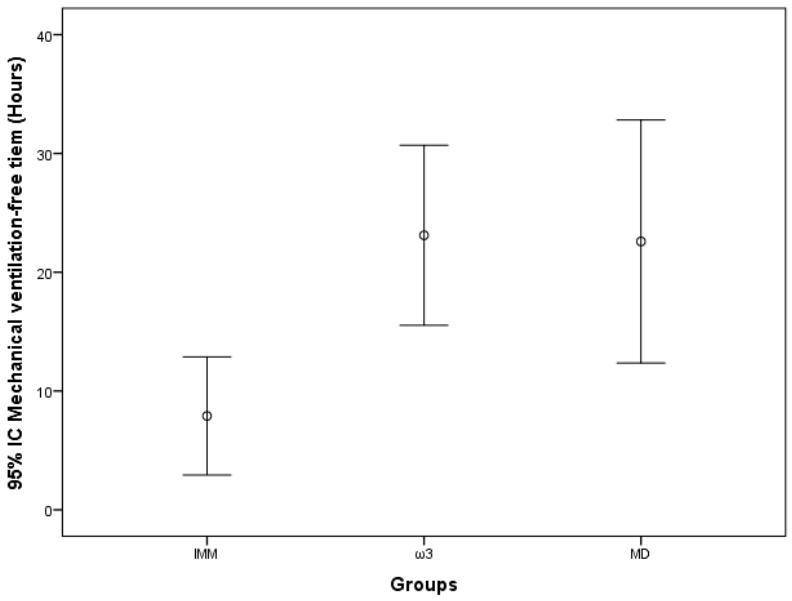

Figure 2. The mechanical ventilation-free time according to different enteral formulae

* $p < 0.01$ compared with IMM and MD