Exploring a tolerable and effective dosage of omege-3 fatty acids as a supplement in enterally fed patients with severe pneumonia: A pilot study

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Running title: Tolerable and effective omega-3 in pneumonia

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ABSTRACT

Background and Objectives: Severe community-acquired pneumonia (CAP) is one of the most common diagnoses in the medical intensive care unit. The objective of this study is to seek an effective and clinically tolerable dosage of ω-3 (EPA+DHA) fatty acids (FA) in enterally fed patients with severe pneumonia. **Methods and Study Design:** A total of 84 patients were randomly assigned to a control group or two experimental groups from January 2022 to June 2024, each receiving 3.50g and 8.75g of ω-3 FA daily for 7 days, and clinical outcomes and tolerance parameters were collected. **Results:** ω-3 FA supplementation significantly reduced mechanical ventilation (MV) duration, hospital expenses, and daily hospital costs. Mechanistically, the anticipated anti-inflammatory effect was not observed but a trend of immune enhancement was noted. The addition of 3.50g and 8.75g of ω-3 FA daily was relatively well-tolerated in patients with severe pneumonia. **Conclusions:** In this pilot study, ω-3 FA supplementation at 3.50–8.75 g/day to enterally fed patients with severe pneumonia for 7 days was relatively well-tolerated, shortened days of MV, and decreased hospital cost. Further investigation with adequate statistical power and larger sample size is warranted to confirm these clinical benefits and establish the optimal dosage for this supplementation strategy.

Key Words: pneumonia, ICU, ω-3 fatty acids, immunonutrition, enteral nutrition, tolerance

INTRODUCTION

Severe community-acquired pneumonia (CAP) is one of the most commonly diagnoses in the medical intensive care unit. It often occurs as a result of infection from one or combinations of pathogens including bacteria, virus and fungi, which could activate innate immune responses and inflammation cascades.[1] Severe pneumonia is associated with high mortality and also leads to various sequelae even if survived.[2] Identifying the causative pathogen is critical in decreasing the mortality and promoting the early and adequate treatment with antibiotics. Therefore, antimicrobial treatment is undoubtedly the principal mode of the treatment. Nevertheless, studies have also found that lower levels of immunoglobulins were associated with increased mortality in ICU patients with severe pneumonia.[3,4] In addition, levels of inflammatory markers, such as interleukin-6 (IL-6) were found to be the most effective predictor of disease severity.[5] Therefore, Adjudicative treatments have also been

used to boost immunity and promote recovery, including immunoglobin treatment and anti-inflammatory/corticosteroids treatment.[2]

Due to the profound influence of coronavirus pandemic, pneumonia has become a focal research point in many fields such as immunonutrition. A recent study has demonstrated that lower levels of plasma ω-3 FA are associated with greater severity of COVID-19.[6] A meta-analysis done on patients with acute lung injury (ALI) concluded that ω-3 FA can effectively improve the respiratory function and promote the overall recovery.[7] One previous meta-analysis focusing on post-operative patients exhibited a clear difference in IgA, IgG, and IgM levels between the ω-3 and control groups on the sixth postoperative day, indicating humoral immunomodulatory function of ω-3 FA.[8] The above results may be explained mechanistically by the anti-inflammatory and immunomodulatory properties of ω-3 FA.[9,10] For instance, ω-3-derived metabolites can turn off the inflammatory response and turn on the healing response that helps the cells repair the damage caused by inflammation.[11]

The intravenous use of ω-3 FA has been well-established in post-operative and ICU patients as evidenced by ESPEN and ASPEN guidelines with exact dosage recommendation of (EPA+DHA)0.1-0.2 g/kg/d.[12,13] A recently published network meta-analysis further confirmed the various clinical advantages of parental ω-3 FA over all other types of intravenous lipid emulsions.[14] However, the benefits of supplementing ω-3 FA in enteral route is controversial, potentially due to the variation in dosages and intervention duration, resulting in conflicting results.[9,15] Research about supplementing ω-3 FA in patients with severe pneumonia is rather scarce. Based on current literature, most ω-3 FA enteral intervention studies used commercially enriched enteral products that claim certain levels of ω-3 FA contents, but often include other imunonutrients such as antioxidants, glutamine or probiotics.[16] Furthermore, the amount of oils present in the product may not be consistent with the amount they claimed.[17,18] Lastly, the tolerance of ω-3 FA containing enteral products compared to that of the standard formulas has been rarely discussed. Therefore, the objective of this study is to seek a clinically effective and tolerable dosage of ω-3 FA as a supplement for patients with severe pneumonia who are enternally fed with standard enteral formula.

MATERIALS AND METHODS

Subjects and study design

The study was a single-centered and single-blinded randomized control study conducted at the Medical Intensive Care Unit of West China Hospital Sichuan University, Chengdu, China from January 2022 to June 2024. The inclusion criteria comprised: aged 18-90 years of age;

primary diagnosis being severe pneumonia; feeding tube-placed and nutrition support solely through enteral route; mechanically ventilated; informed consent signed by patients' family members/legal representatives. The exclusion criterion included: signs or evidence of gastrointestinal bleeding; nutrition support not solely on enteral route; reported allergy to ω-3 FA containing products; diarrhea; pregnancy/breastfeeding; surgery history in recent 3 months; diagnosis of cancer; severe impairment of kidney and/or liver function. Criterion to withdraw included: a physician's order to withdraw, usually due to gastrointestinal (GI) dysfunction including but not limited to active GI bleeding, abdominal distention, emesis or other adverse effects occurred during intervention; families/legal representative requested to withdraw from the study due to personal or financial factors (Figure 1).

Determination of sample size and group assignment

Since ICU length of stay (ICU-LOS) was one of the most reported positive results from many previous studies,[7,19,20] we referred this parameter in calculating the sample size. According to the findings of Rice et al[21], the mean ICU-LOS was 14 ± 10.5 days in the intervention group and 16.7 ± 9.5 days in the control group. Pontes-Arruda et al[22] reported 28-day ICU-free days of 10.8 ± 1.1 versus 4.6 ± 0.9, from which the ICU stay was back-calculated. Pooling these two studies, we set the mean ICU stay for the low-dose group at 15.5 days and for the control group at 19.9 days. The high-dose group was estimated to have a mean ICU stay of 10.5 days, with the standard deviation set at the largest reported value of 10.5. Sample size was calculated using PASS 15.0 (One-Way ANOVA F-test) with $\alpha = 0.05$ and $\beta = 0.20$, yielding a minimum of 26 participants per arm. Accounting for a potential dropout rate of 10%, a total of 29 participants per group are planned to be enrolled, ensuring that the final valid sample size exceeds 26 per group.

Intervention

Enteral nutrition therapy was initiated within 24 h of admission, unless ordered to postpone according to the ESPEN and ASPEN guidelines. Since indirect calorimetry is not adequately available in our institution, the caloric targets of the patients were estimated using the simple weight-based equations based on the patients' ideal weight timing: 30kcal/kg suggested by ESPEN guideline.[23] The intervention period is 7 feeding days, the standard time used by the majority of the studies done on septic ICU patients.[15] Patients who failed to meet the required 7-day dosage of administration due to operations, procedures or prone position were fed continuously until they finish the target 7-day feeding regimen.

The formula used for the control and intervention groups was a normocaloric standard enteral formula with 478 kcal calories, 18.5 g of protein and 17.5 g of fat per 100 g of product. The formula, in powder form, was re-hydrated and transferred into sterile feeding bags in the designated preparation room and sent to the intensive care units before administration (Pump-assisted bolus tube feeding, target rate at 120 mL/h, Quater in die). In the intervention groups, the ω-3 FA supplement, also in powder form, was added and mixed evenly into the standard formula during the process of rehydration. The interventional dosages of ω-3 FA were decided by referring the International Society for the Study of fatty acids and Lipids (ISSFAL)[24] and ESPEN expert group on the lipids in the intensive care unit.[25] The ISSFAL considers a daily dose of 1.50 g to 3.50g as a high dose in ICU patients; therefore, 3.50 g was set as the first interventional dosage level.[24] Considering the safety, the second interventional dosage was calculated using the average daily intervention dosages of the interventional studies referred in the recommendations from ESPEN expert group on the lipids in the intensive care unit, except two studies with surgical patients as the study population, which turned out to be 8.68g/d (Supplementary Material 1).[25] The two levels of interventional dosage were designed to expect a dose dependent effect. The ω-3 FA product (Lingli Duobang, Blue Regale Medical Technology Co., Ltd, Suzhou, China) used in the intervention contains 1.75 g of ω-3 FA(EPA+DHA)/pack; therefore, 2 packs (3.50 g) and 5 packs (8.75 g) was used during the re-hydration process.

This research adhered to ethical guidelines from the Declaration of Helsinki. Prior to commencing the study, the research protocol was approved by the ethics committee of the responsible medical research institution (West China Hospital Sichuan University, Chengdu, China). Written informed consent was obtained from the patients or their family members/legal representatives if non-autonomous. The study was registered at Official Clinical Trial Registry in the WHO (World Health Organization) registry network. Study ID: ChiCTR2100043173 www.chictr.org.cn/indexEN.html

Data collection

Data was collected by three stakeholders on our team, attending physicians, nurses and dietitians. The nurses input the anthropometric and demographics information upon admission. In addition, they also recorded the gastric residue volume (GRV) and stool volume of the patients as a part of their care notes. The dietitians recorded each patient's nutrition regimen daily and recorded the relevant laboratory values. The attending physicians completed the

Acute Physioology and Chronic Health Evaluation II (APACHE II) evaluation and prescribe laboratory tests as needed.

The demographic data included age, sex, and APACHE II scores. Anthropometric measurements recorded were weight (kg), height (cm) and calculated BMI (kg/m^2). Baseline laboratory tests were conducted within 24 hours prior to the first day of intervention, including nutrition markers (hemoglobin, prealbumin), inflammatory parameters (C-reactive protein, PCT, IL-6) and immunity parameters (IgG, IgM, IgA). The above lab values were collected again within 24 hours after patients completed the intervention. Clinical outcomes were collected including in-hospital deaths, types of discharge (premature or stabilized), days of MV (mechanical ventilation), LOS, ICU-LOS, total hospital expenses and daily hospital expenses. Premature discharge occurred when the family members/legal representatives voluntarily withdrew the hospitalization despite optimistic prognosis, usually due to the patient's financial difficulties or religious beliefs.

In terms of tolerance parameters, since there is no universally accepted definition of feeding intolerance (FI), the proposed definition from a recently published systematic review were referenced which includes failure to reach EN targets and the presence of gastrointestinal symptoms.[26] Although some of the guidelines (e.g. ASPEN) does not recommend routinely checking gastric residue volume, the majority of current studies (74/89) still use GRV as the one definition of FI.[26] In this current study, gastric negative pressure suction was routinely conducted when the nurse found the patient with abdominal distention prior to each feeding. A recently published review article concluded that observing large-GRV-centered gastrointestinal symptoms are more effective than feeding insufficiency as a tolerance definition.[27] Therefore, the GRV recorded was related to symptom of abdominal distention, which were seen as the one sign of FI. The other FI parameter was the sign of diarrhea, which in this study was defined solely by stool volume. This is because the fecal incontinence pouch is routinely used in this care unit to prevent pressure ulcers and reduce nurses' workload; consequently, stool frequency and consistency were not included as indicators of diarrhea. (Supplementary Material 2). The third tolerance parameter, feeding adequacy, was calculated from the actual feeding energy (highest during the intervention period) divided by patients' target energy needs multiplied by 100%.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 27 (IBM Corp., Armonk, NY, USA) and PASS 15.0 (NCSS Statistical Software, Kaysville, UT, USA).

The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Baseline data, age, APACHE II score, BMIs, baseline lab values are presented in the form of means and standard deviations (SDs) or (One-way ANOVA) or medians (25 percentiles, 75 percentile) (Kruskal-Wallis Test). Descriptive statistics such as sex is used for categorical data, presented as n (%), with differences in group distributions compared using the Chi-Squared test. Clinical outcomes including LOS, ICU-LOS, hospital expenses, days of MV and discharge types were compared by the Kruskal-Wallis test and Chi-Squared test. Both the LOS and ICU-LOS was analyzed twice with and without premature discharged patients (Table 3b). Tolerance parameters including the GRV, stool volume and feeding adequacy were also compared using one-way ANOVA or Kruskal-Wallis Test depending on the distribution of the data. The significance level was set at $\alpha = 0.05$, and a p value less than 0.05 indicated a statistically significant difference.

RESULTS

After screening and exclusion (n = 112), a total of 93 eligible patients were consecutively recruited into the trial. During the intervention process, 9 patients withdrew, resulting in 84 patients ultimately completing the intervention (Figure 1). The study cohort was comprised of 60 males and 24 females, with a mean age of 65 ± 14.85 years. The mean BMI were 22.45 ± 12.2 kg/m^2, and were not different between three groups. The energy targets of the patients were not different between groups either, which was around 1767kcal/d. In respect to disease severity, the APACHE II scores were also not statistically different between groups with an average score of 18.88 ± 7.57. The baseline laboratory test results in including nutrition markers (hemoglobin, prealbumin), inflammatory parameters (C-reactive protein, PCT, IL-6) and immunity parameters (IgG, IgM, IgA) were all not different between groups as shown in Table 1.

Nutrient intake

In terms of the nutrition intake, the energy and protein were all the same among the three groups with the daily average energy intake of 1750.7 ± 254.0 kcal and 66.33 ± 9.7g of protein per day. In terms of the fat content, due to the higher ω-3 FA intervention dosage, the fat content of the 8.75 g group is significantly higher than the control and the 3.50 g group (p <0.001) (Table 2). Since significant differences in fat content were observed, we performed a statistical adjustment and reanalyzed all clinical outcomes. The results showed that hospital

expenses and days of MV remained consistently significant. However, among the mechanistic parameters, the previously observed increase in IL-6 disappeared after adjustment.

Primary outcomes

Initially, no significant differences were observed among groups for any of the investigated clinical outcomes, including LOS, ICU-LOS, daily hospital expenses, duration of mechanical ventilation (MV), and in-hospital outcomes. Nevertheless, we considered the imbalance in baseline APACHE II scores to be clinically important although they did not differ statistically among the three groups (p >0.05). Therefore, a sensitivity analysis was performed using propensity score methods to adjust for the potential confounding effect of APACHE II score on clinical outcomes. Propensity score methods are particularly suitable when sample sizes are small or assumptions for analysis of covariance are violated. Inverse probability weighting was employed, with propensity scores calculated using the APACHE II variable.

After adjusting the APACHE II scores, propensity score analysis revealed significant differences in Hospital expenses, Daily hospital expenses, Days of MV, In-hospital clinical outcome, IL-6, IgA, and GRV between groups (Table 3b, Table 4b & Table 5b). This indicates that baseline differences in APACHE II scores had confounded the initial analysis, explaining the previous null findings.

To confirm the difference between groups, post-hoc comparisons were performed using the new version of the non-parametric test menu, with the Bonferroni method applied to adjust the significance level (adjusted $\alpha = 0.0167$). For hospital expenses, the control group spent significant more than the 3.50g FA group, but not the 8.75g FA group ($p = 0.001$). Similarly, the control group had higher daily expenses than the 3.50 FA group, but not the 8.75g FA group ($p = 0.011$). Regarding the days of MV, the control group had longer duration than both the 3.50g FA group and 8.75g FA group ($p = 0.009$). For in-hospital clinical outcome, pairwise chi square comparisons showed no statistically significant differences between groups at the α=0.0167 level.

With respect all the laboratory values, the initial analysis of changes (δ = out-in) in the investigated values were not different between groups (Table 4a), therefore we also applied the sensitivity test in these secondary outcomes. After adjusting the APACHE II scores, the IgA and IL-6 turn out to be statistically significant ($p = 0.044$ and $p = 0.043$) (Table 4b) however, the Post-hoc comparisons revealed non-significant differences in IgA and IL-6 between groups at the $\alpha = 0.0167$ level.

In the context of tolerance parameters, also after adjusting APACHE II score, stool volume and feeding adequacy were not significant different between three groups (Table 5b). However, the GRV of the control group is significantly higher than both the experimental groups ($p = 0.039$). Most of the patients were fed adequately, as the feeding adequacy of three groups were 0.95 ± 0.17, 1 ± 0.16, 1.01 ± 0.24 with $p = 0.074$.

DISCUSSION

In this current study, the efficacy and tolerance of adding two dosages ω-3 FA(EPA+DHA) in regularly fed patients on standard enteral formula was explored. This is the first study that investigated both the effectiveness and tolerance of administrating ω-3 FA in regularly fed patients with severe pneumonia on standard enteral formula.

Efficacy

With regard to the efficacy, we found no statistical significance in primary outcomes including LOS, ICU-LOS and in-hospital clinical outcome. The number of in-hospital deaths (3/28) of our patients were the same across all three groups, which corresponded well with Koekkoek et al's meta-analysis where they found no evidence for improved mortality from enteral fish oil supplementation among critically ill patients.[9] These non-significant endpoint results are also in line with the current literature that enteral immunonutrition formulas may be beneficial to the trauma and surgical patients but controversial in internal medical patients.[10] As the primary outcome ICU-LOS did not differ significantly among the three groups, we conducted a post-hoc power analysis, which yielded a power of only 38.79. This suggests that the some of the negative findings may stem from insufficient sample size and underscores the need to expand enrollment in future studies.

Nevertheless, we demonstrated significantly lower total hospital expenses, daily expenses, and shorter MV duration in the intervention group(s). The differences in hospital expenses and days of MV remained statistically significant after adjusting for total fat intake ($p = 0.023$ and 0.036, respectively). These findings are robust and confirm that the clinical benefits observed are directly linked to ω-3 FA supplementation, independent of the concurrent increase in total dietary fat. The reduced MV days align with prior meta-analyses identifying MV duration as a key improved process parameter in ω-3 FA-supplemented patients.[9,15] Regarding cost savings, most comparable studies utilized parenteral administration.[28,29,30] Our findings provide novel evidence for the cost-saving effects of enteral ω-3 FA supplementation. While not altering clinical endpoints such as LOS or mortality, ω-3 FA

supplementation reduced patient burden through shorter MV duration and alleviated family and healthcare economic strain.

Considering the underlying mechanistically benefits of ω-3 FA in shortening the MV and decreasing the hospital cost, namely, the immunomodulatory effect and the anti-inflammation effect, were not clearly observed in this study. Nevertheless, promising the immunomodulatory trends were noted, with IgA and IgM levels showing stepwise improvement as the ω-3 FA dosage increased, although non-significant, shown in Table 4. Paradoxically, inflammatory markers presented an unexpected pattern: IL-6 levels rose with higher ω-3 FA dosages, suggesting a potential adverse inflammatory response in this patient group. Keokkoek et al, have previously suggested that the anti-inflammatory effects of ω-3 FA may be most beneficial to the sickest patients but may be detrimental in less severely ill patients.[9] These findings also align with a recent meta-analysis,[31] which noted that ω-3 FAs, while beneficial during hyper-inflammation, may suppress immunity during hypo-inflammation. In our study subjects with relatively lower inflammation, high-dose ω-3 FAs may have over-corrected the response, inadvertently suppressing innate immunity and potentially leading to the observed higher IL-6 levels. Furthermore, the fact that this inflammatory rebound vanished after adjusting for total fat intake suggests that the high fat content of the dietary regimen itself may have exerted a pro-inflammatory effect. In conclusion, the observed escalation in inflammation in our study may be a composite result of both the over-correction of inflammation by high-dose ω-3 FAs and the pro-inflammatory influence of a high-fat dietary pattern.

Contemplating the insights from previous studies and results from our study, it can be speculated that ω-3 FA tend to improve immune function in internal medical patients while attenuate inflammation in the most critically ill patients with acute inflammation. The clinical impact of improved immune function may be less immediately evident than the resolution of acute inflammation, which could explain why positive outcomes of ω-3 FA supplementation have been more consistently reported in acute conditions such as trauma, ALI and acute respiratory distress syndrome (ARDS) patients.[19,21,32]

Tolerance, clinical and socioeconomic significance

In regard to tolerance, most of the patients were adequately fed and no adverse effects such as diarrhea, dysgeusia, and bleeding tendency, etc.33 Additionally, the intervention did not increase GRV or stool output, nor did it compromise feeding adequacy. Interestingly, GRV was significantly higher in the control group. This may be attributed to inaccurate assessment

of actual GRV associated with gastrointestinal symptoms other than abdominal distension, a limitation noted in this study. Although well tolerated in this small cohort, the dosage of 8.75 g ω-3 FA remains exploratory. Further investigation is needed to clarify its safety profile and potential pro inflammatory effects in medical intensive care patients.

Still, the current positive tolerance results from this study holds both clinical and socioeconomic significance. In addition to the previously discussed clinical benefits of shortened MV and reduced cost, socioeconomically, adding ω-3 FA as a supplemental module into the currently available basic standard EN feeding provides a flexible and practical way of allowing the patients from developing countries to also obtain the benefits of ω-3 FA. The development of medical foods in China is far behind that of developed countries. The supply of food for medical purposes (FSMPs) from local production does not meet the demand from widespread malnutrition of patients in China.[34,35] As one study reported, 65% of the malnourished patients in the United States received FSMPs, but merely 1.6% of such patients did in China.[36] In addition to the supply deficit, the variety of FSMPs is also much less than that in developed counties. Most previous research on ω-3 FA was done using the ω-3 FA enriched enteral products such as Oxepa and Recovan, which are not available in China.[12,37,38] One previous study that used 1000mg of ω-3 FO as a supplemental module for regular EN was also conducted from a developing country.[39] Currently, the majority of available enteral products are basic formulas intended for a broader spectrum of applications across various groups of patients and the specialized formulas with immune-modulating and other health benefits remain underdeveloped. Therefore, the current findings regarding clinical benefits and feeding tolerance provide preliminary data to support larger-scale studies aimed at further exploring the clinical efficacy and optimal dosage of this supplementation strategy.

Limitations

The current study encountered several limitations that warrant acknowledgment. The primary limitation is the small sample size. Post-hoc power calculations indicated that the statistical power of our analyses was relatively low. Although clinical benefits were observed after adjusting for APACHE II scores, larger studies are needed to confirm these findings. Another limitation relates to the measurement of GRV, which was recorded only when abdominal distension was present. This approach may have underestimated actual GRV associated with other GI symptoms listed in ESPEN guideline.[23] Additionally, while the dosage of 8.75 g/day ω-3 FA was well tolerated in this cohort, its potential adverse effect on inflammation warrants

caution when determining the upper intervention limit. A further limitation is the significantly higher fat content in the 8.75 g/day ω-3 group ($p < 0.001$), resulting from the lack of adjustment to the base enteral formula. This may have introduced a confounding variable, as a high-fat diet could be inherently more pro-inflammatory than a normal-fat diet.[40,41] While statistical adjustments were made in the current study to account for potential confounders, future large-scale investigations are warranted to eliminate these variables at the design stage by incorporating a placebo control group. Moreover, this was a short-term, single-center pilot study. The limited follow-up period may have been insufficient to capture the full impact of the intervention, as survival benefits often require longer observation windows to become measurable. Therefore, future research with larger sample sizes, multi-center collaboration, and extended follow-up is encouraged to fully elucidate the potential benefits of this intervention.

Conclusion

In this study, we investigated the effects of ω-3 FA (EPA+DHA) as a nutritional supplement in patients with severe pneumonia receiving enteral nutrition. Enteral administration of ω-3 FA at daily doses ranging from 3.50 g to 8.75 g was generally well tolerated and showed positive clinical benefits, including reduced hospital costs and shorter duration of MV. Mechanistically, the anticipated anti-inflammatory effect was not clearly observed; however, a trend toward immune improvement was noted. Further studies with larger sample sizes are warranted to better define the clinical benefits and optimal dosing of this supplementation strategy.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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collection, analysis, and interpretation of results were conducted independently and without any influence from the company. The researchers maintained full autonomy throughout the study to ensure the integrity and objectivity of the findings. The sponsor had no role in the decision to publish or preparation of the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Kimi.ai in order to improve the readability and language of the manuscript exclusively for language polishing and grammar correction. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article

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Table 1. Clinical characteristics according to different enteral formula (numbers and percentages; means and standard deviations; medians and interquartile range)

	Total (n=84)	Control (n=28)	3.50g dose (n=28)	8.75g dose (n=28)	χ^2/F	*p* values
Sex, n (%)					1.05	0.592
Male	60 (71)	19 (68)	22 (79)	19 (68)		
Female	24 (29)	9 (32)	6 (21)	9 (32)		
Age ± SD (years)	65.6 ± 14.85	64.61 ± 17.48	67.29 ± 12.77	64.89 ± 14.3	0.27	0.764
APACHE II	18.88 ± 7.57	20.14 ± 7.32	19.68 ± 8.02	16.82 ± 7.16	1.604	0.208
Height (cm)	163.90 ± 7.197	165.07 ± 7.044	163.46 ± 7.23	163.18 ± 7.42		
Weight (kg)	60.43 ± 12.195	61.48 ± 10.86	60.79 ± 12.33	59.01 ± 13.56		
BMI (kg/㎡)	22.45 ± 4.33	22.60 ± 4.68	22.77 ± 4.68	22.02 ± 4.33	0.225	0.799
Nutrition (energy) targets (kcal)	1767.14 ± 215.91	1802.14 ± 211.33	1745.36 ± 222.72	1745.36 ± 222.72	0.557	0.575
Laboratory values						
HGB (g/L)	93.50 (81.25, 110.00)	88.5 (70.75, 114)	91 (83.25, 100.5)	101.50 (89, 116.25)	4.004	0.135
Prealbumin (mg/L)	135.5 (87.03, 135.5)	144 (79.55,187.25)	121.5 (73.25, 166.25)	135.5 (107, 167.75)	0.847	0.655
IgG (g/L)	10.65 (7.78, 13.558)	10.065 (7.32, 13.175)	9.355 (7.29, 9.35)	10.5 (8.4, 13.375)	0.530	0.767
IgA (mg/L)	2395 (1482.5, 3325.0)	2545 (1457, 3465)	2290 (1360, 2975)	2425 (1505, 3802)	0.857	0.651
IgM (mg/L)	765 (507, 1227)	790 (607.5, 1027.5)	751 (507, 1070)	805 (460.25, 1727.5)	0.142	0.931
PCT (ng/mL)	0.225 (0.123, 0.635)	0.26 (0.15, 0.76)	0.235 (0.12, 0.54)	0.15 (0.1, 0.43)	.0384	0.184
CRP (mg/mL)	46.2 (15.4, 99.0)	67.25 (14.625, 105)	49.5 (26.65.99)	32.5 (12, 87.675)	2.074	0.355
IL-6 (pg/mL)	25.15 (13.15, 89.325)	22.25 (12.575, 83.225)	23.4 (16.8, 106.875)	35.9 (11.625, 83.175)	0.417	0.812

APACHE II, Acute Physiology and Chronic Health Evaluation.Nutrition targets were estimated by weight-based equations using patients' ideal weight timing 30kcal/kg.

Table 2. Nutrition intake of control group and intervention groups

	Total	Control	3.50 g/d	8.75 g/d	χ^2/F	*p* values
Energy (kcal/d)	1750.73±254.0	1684.64±232.9	1762.21±180.9	1805.32±321.9	1.648	0.199
Protein (g/d)	66.33±9.7	65.20±9.0	66.98±7.0	66.82±12.4	0.286	0.752
Fat (g/d)	66.92±10.1	61.68±8.5	66.86±6.6	72.21±11.78	9.123	<0.001

Values were shown as means±SD.

Table 3. Clinical outcomes of control group and intervention groups (with and without sensitivity analysis)

	Total (n=84)	Control (n=28)	3.50g dose (n=28)	8.75g dose (n=28)	χ^2/F	*p* values
Without sensitivity analysis					1.05	0.592
LOS (days)	32 (24, 47)	36 (26, 50.75)	30.5 (24.75, 43.5)	30 (23, 41)	1.875	0.392
ICU LOS (days)	19.00 (13.0, 28.5)	21.5 (15, 38.75)	20.0 (11.25, 26.50)	16 (13.00, 25.5)	1.176	0.555
Hospital expenses (Chinese Yuan)	189168 (125025.25, 282435.25)	216538.07 (151732.25, 350740.25)	145145 (98901.75, 235383)	198030 (128196, 261606.5)	4.85	0.088
Daily hospital expenses (Chinese Yuan)	5752.95 (4000.9, 7302.67)	5926.18 (4635.76, 7878.29)	5343.29 (3356.05, 6119.26)	6142.89 (3526.79, 8497.7)	3.613	0.164
Days of mechanical ventilation	14 (8.5, 22)	20 (12.5, 32)	13 (7.75, 21.25)	12 (8, 20)	4.419	0.11
In-hospital clinical outcome, n(%)					4.333	0.351
Death (In-hospital)	9 (11)	3 (11)	3 (11)	3 (11)		
Premature discharge	30 (36)	9 (32)	7 (25)	14 (50)		
Discharged with stabilized condition	45 (54)	16 (57)	18 (64)	11 (39)		
With sensitivity analysis						
LOS (days)	32 (24, 47)	36 (26, 50.75)	30.5 (24.75, 43.5)	30 (23, 41)	4.940	0.085
Premature discharge excluded	33(25, 49)	38 (25, 54)	32 (25, 49)	31 (24, 47)	1.365	0.505
ICU LOS (days)	19.00 (13.0, 28.5)	21.5 (15, 38.75)	20.0 (11.25, 26.50)	16 (13.00, 25.5)	2.738	0.254
Premature discharge excluded	18 (13,26)	20.5 (14.25, 40)	18 (11, 25.5)	16 (13, 23)	1.498	0.473
Hospital expenses (Chinese Yuan)	189168 (125025.25, 282435.25)	216538.07 (151732.25, 350740.25)[a]	145145 (98901.75, 235383)[b]	198030 (128196, 261606.5)[a]	13.431	0.001
Daily hospital expenses (Chinese Yuan)	5752.95 (4000.9, 7302.67)	5926.18 (4635.76, 7878.29)[a]	5343.29 (3356.05, 6119.26)[b]	6142.89 (3526.79, 8497.7)[a]	8.959	0.011
Days of mechanical ventilation	14 (8.5, 22)	20 (12.5, 32)[a]	13 (7.75, 21.25)[b]	12 (8, 20)[b]	9.326	0.009
In-hospital clinical outcome, n (%)					13.185	0.010
Death (In-hospital)	9 (11)	3 (11)	3 (11)	3 (11)		
Premature discharge	30 (36)	9 (32)	7 (25)	14 (50)		
Discharged with stabilized condition	45 (54)	16 (57)	18 (64)	11 (39)		

The exchange rate of Chinese Yuan stood at 7.1889 against the US Dollar, 7.4562 against the Euro, and 8.8557 against the British Pound by the day of January 17, 2025..

Table 4. Changes of laboratory tests. Measurement of markers of nutrition, immunology and inflammation (with and without sensitivity analysis)

Lab measures	Control (n=28)	3.50g dose (n=28)	8.75g dose (n=28)	χ^2/F	*p* values
Without sensitivity analysis					
HGB (g/L)	2.93 ± 14.79	0.64 ± 13.57	2.82 ± 16.88	0.203	0.817
Prealbumin (mg/L)	-15.2 (-87.97, 48.5)	-12 (-89, 15.18)	3 (-75.5, 31.75)	0.11	0.946
IgG (g/L)	-0.82 (-3.79, 0.16)	-1.15 (-2.07, 0.59)	-0.68 (-2.69, 3.19)	1.119	0.572
IgA (mg/L)	-190 (-496.75, 192.5)	-105 (-292.5, 120)	70 (-437.5, 557.5)	1.823	0.402
IgM (mg/L)	-37.5 (-241.5, 139.25)	-28.5 (-203.5, 69.5)	18.5 (-202.5, 104)	0.923	0.63
PCT (ng/mL)	0.02 (-0.14, 0.24)	0.05 (-0.2, 0.13)	0.01 (-0.1, 0.22)	0.074	0.964
CRP (mg/mL)	10.11 (-27.8, 61.94)	12.7 (-2.38, 48.62)	1.16 (-17.85, 33.3)	0.432	0.806
IL-6 (pg/mL)	0.2 (-47.37, 14.81)	2.5 (-22.24, 17.02)	4.8 (-8.12, 42.81)	1.953	0.377
With sensitivity analysis					
HGB (g/L)	2.93 ± 14.79	0.64 ± 13.57	2.82 ± 16.88	0.817	0.443
Prealbumin (mg/L)	-15.2 (-87.97, 48.5)	-12 (-89, 15.18)	3 (-75.5, 31.75)	0.344	0.842
IgG (g/L)	-0.82 (-3.79, 0.16)	-1.15 (-2.07, 0.59)	-0.68 (-2.69, 3.19)	3.549	0.170
IgA (mg/L)	-190 (-496.75, 192.5)	-105 (-292.5, 120)	70 (-437.5, 557.5)	6.233	0.044
IgM (mg/L)	-37.5 (-241.5, 139.25)	-28.5 (-203.5, 69.5)	18.5 (-202.5, 104)	3.446	0.178
PCT (ng/mL)	0.02 (-0.14, 0.24)	0.05 (-0.2, 0.13)	0.01 (-0.1, 0.22)	0.523	0.770
CRP (mg/mL)	10.11 (-27.8, 61.94)	12.7 (-2.38, 48.62)	1.16 (-17.85, 33.3)	1.342	0.511
IL-6 (pg/mL)	0.2 (-47.37, 14.81)	2.5 (-22.24, 17.02)	4.8 (-8.12, 42.81)	6.303	0.043

The values of the laboratory results were obtained by subtracting the values of the first tests from those of the second tests. The observed laboratory parameters among the three groups are all non-significant different.

Table 5. Comparison of feeding tolerance including stool volume, gastric residue volume, feeding adequacy and incidence of abdominal distention (with and without sensitivity analysis)

Tolerance parameters	Control (n=28)	3.50g dose (n=28)	8.75g dose (n=28)	χ^2/F	*p* values
Without sensitivity analysis					
Stool volume (mL)	550 (350, 1200)	785 (375, 1412.5)	600 (300, 900)	1.446	0.485
GRV (mL)	460 (100, 790)	110 (0, 532.5)	155 (60, 820)	1.947	*p* values
Feeding adequacy (%)	0.95 ± 0.17	1 ± 0.16	1.01 ± 0.24	0.879	0.419
With sensitivity analysis					
Stool volume (mL)	550 (350, 1200)	785 (375, 1412.5)	600 (300, 900)	4.782	0.092
GRV (mL)	460 (100, 790) [a]	110 (0, 532.5) [b]	155 (60, 820) [b]	6.507	0.039
Feeding adequacy (%)	0.95 ± 0.17	1 ± 0.16	1.01 ± 0.24	2.629	0.074

GRV, gastric residue volume, recorded when the nurse observed abdominal distention conducted gastric negative pressure suction prior to each feeding session. The three aspects of feeding tolerance, including stool mass, GRV and feeding adequacy among the three groups were all non-significant different.

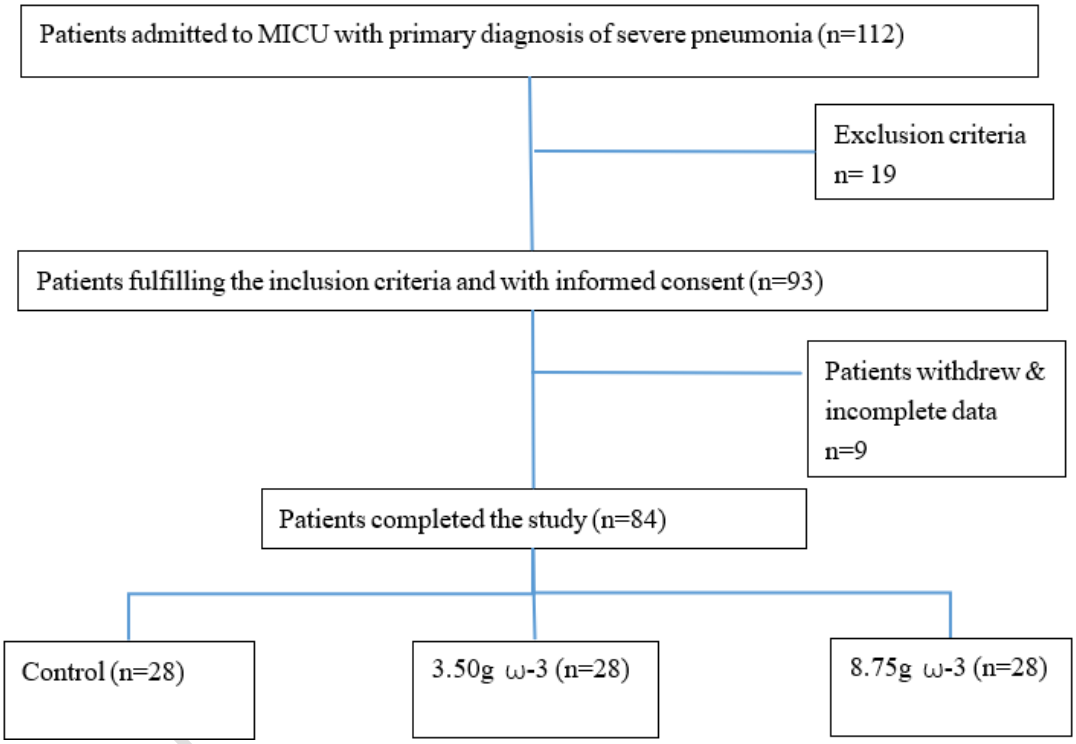

Figure 1. The flowchart of recruitment