Int J Nutr Sci 2026;11(3):508-516

International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

ORIGINAL ARTICLE

Development of an Anti-inflammatory Oral Nutrition Supplement Formula in Critically Ill Patients Admitted to Intensive Care Unit: A Double Blind Randomized Protocol Study

Sajedeh Jandari[1,2], Ahmad Bagheri Moghaddam[3], Alireza Sedaghat[3], Melika Hadizadeh[2], Kimia Kalali Nasrabadi[2], Samira Mowdoudi[1], James R. Hébert[4,5], Hamed Tabesh[6], Mohammad Safarian[1], Mohammadreza Abbaspour[7], Majid Ghayour-Mobarhan[1], Reza Rezvani[1]*

1. Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2. Department of Nutrition, Varastegan Institute for Medical Sciences, Mashhad, Iran
3. Service of Intensive Care Medicine, Emam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
4. Cancer Prevention and Control Program, University of South Carolina, Columbia, South Carolina, USA
5. Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, USA
6. Department of Medical Informatics, Mashhad University of Medical Sciences, Mashhad, Iran
7. Department of Pharmaceutics, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Keywords:
Anti-inflammatory
Nutrition
Oral supplement
Intensive care unit
Please cite this article as: Jandari

**Corresponding author:*
Reza Rezvani, PhD;
Department of Nutrition,
Faculty of Medicine,
Mashhad University of Medical Sciences,
Mashhad, Iran.
Email: RezvaniR@mums.ac.ir
Received: May 8, 2026
Revised: August 1, 2026
Accepted: August 8, 2026

ABSTRACT

Background: Critical illnesses such as sepsis and acute respiratory distress syndrome (ARDS) can lead to organ dysfunction and high mortality and present significant challenges in in intensive care units (ICUs). Current research highlights the importance of nutritional support in managing inflammation and immune response. This study developed a novel anti-inflammatory formula targeting inflammatory markers in ICU patients.

Methods: Seventy-four critically ill adult patients were randomly divided into two groups within 24-48 hours of ICU admission. Two treatment interventions were used; while the control group received the standard oral nutritional supplement (ONS) formula as two times gavage meal, and the intervention group received an anti-inflammatory formula with a low inflammatory profile in the same way as control group for 14 days. Data collection were included demographic information and blood samples at baseline, day 7, and day 14.

Results: Nutritional intervention in modulating inflammation and immune response in critically ill patients, particularly those experiencing systemic inflammatory response syndrome (SIRS) or sepsis was verified.

Conclusion: This study considering the efficacy of low inflammatory index formulas and their effects on clinical outcomes in critically ill trauma patients.

S, Bagheri Moghaddam A, Sedaghat AR, Hadizadeh M, Kalali Nasrabadi K, Mowdoudi S, Hébert JR, Tabesh H, Safarian M, Abbaspour MR, Ghayour-Mobarhan M, Rezvani R. Development of an Anti-inflammatory Oral Nutrition Supplement Formula in Critically Ill Patients Admitted to Intensive Care Unit. Int J Nutr Sci. . Int J Nutr Sci. 2026;11(3):508-516. doi: 10.30476/ijns.2026.106604.1453.

Introduction

Critical illness, including conditions such as sepsis and acute respiratory distress syndrome (ARDS), poses significant challenges in intensive care units (ICUs) worldwide. Patients with these conditions often experience dysregulated immune responses and excessive inflammation, leading to organ dysfunction and high mortality rates (1-4). Recent studies have shown that nutritional support plays a crucial role in modulating inflammatory processes, antioxidant status, and overall immune function (5, 6). Nutrients such as amino acids, antioxidants, minerals, and fatty acids have shown promising effects in reducing inflammation and improving clinical outcomes in surgical, injured, and critically ill patients (7, 8).

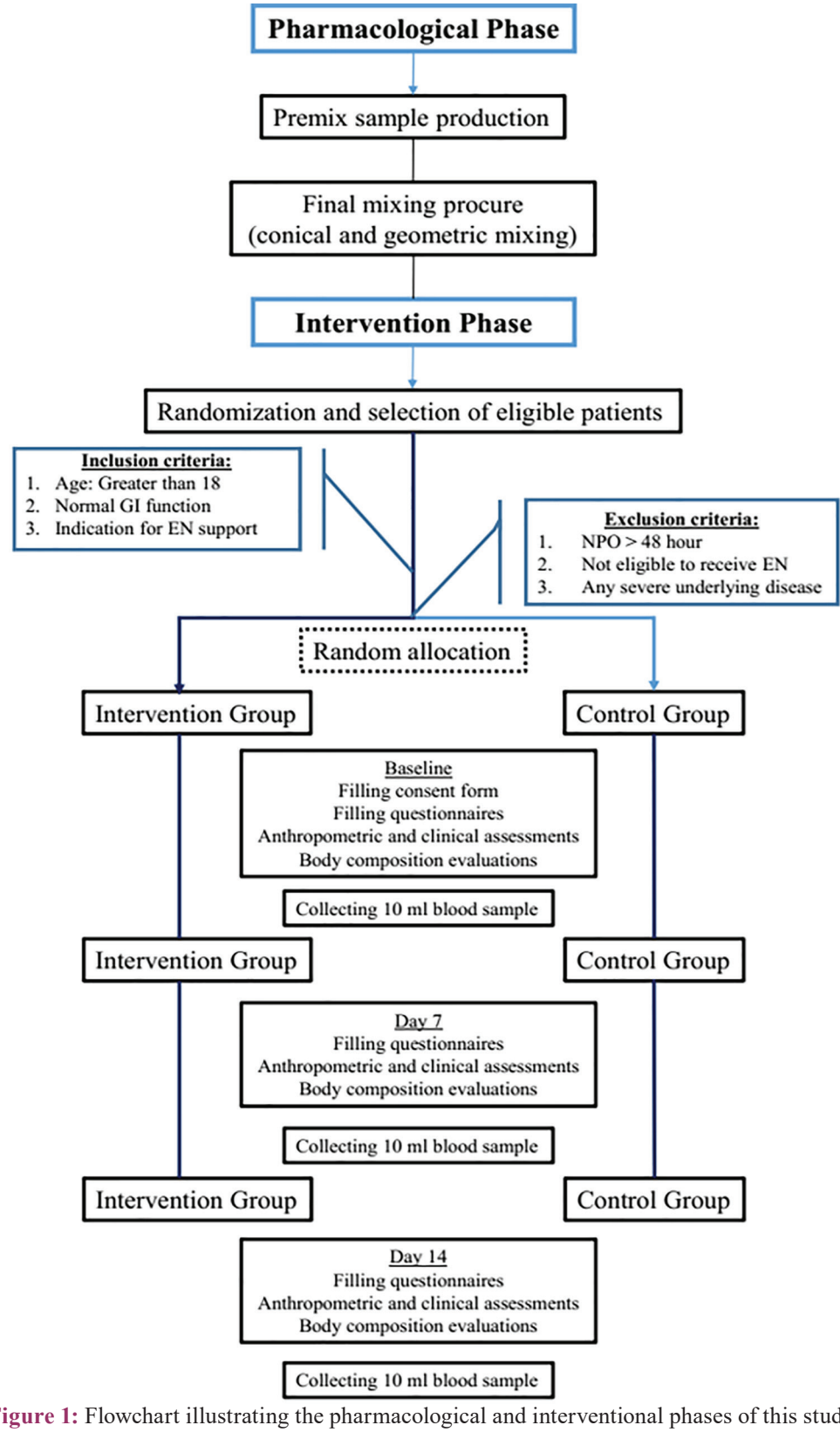

Figure 1: Flowchart illustrating the pharmacological and interventional phases of this study.

However, the effectiveness of immunonutrition formulations in critically ill patients remains a topic of debate (9-14). While previous studies have demonstrated the benefits of immunonutrition formulations containing these nutrients, their effectiveness in ICU patients remains uncertain, highlighting the need for further investigation (15, 16).

A novel anti-inflammatory formula based on the Dietary Inflammatory Index (DII®) has been developed to target inflammatory markers in ICU patients (17, 18). This formula was shown to be based on anti-inflammatory low dietary inflammatory index (low-DII) score formula. It focused on specific anti-inflammatory substances with negative inflammatory index scores, including vitamins, minerals, and medical nutrients (nutraceuticals) within recommended daily allowances (RDA) and upper limits (UL). This formula was utilized in neurosurgery and head trauma units demonstrated promising results in reducing inflammation and improving clinical parameters (18).

To validate and refine these findings, a larger-scale study was designed involving critically ill patients admitted to general ICUs. Building on insights gained from a previous study (18), our strategy involved a two-phase approach including a pharmacological phase and an interventional phase. During the interventional phase, our objective is to assess the impact of our anti-inflammatory formula on inflammatory markers, antioxidant status, and clinical outcomes in critically ill patients. Specifically, we aim to investigate the efficacy of this novel anti-inflammatory oral nutritional supplement in ICU patients, targeting specific inflammatory pathways to improve patient outcomes. This protocol study develops evidence-based strategies to help modulate inflammation, enhance antioxidant defenses, and improve clinical outcomes in these vulnerable patients.

Materials and Methods

The protocol for this study was developed in adherence to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 reporting guidelines (19). A visual flowchart of the trial's enrollment, interventions, and assessments were presented in Figure 1. Study visits were planned for days 1 through 14 in order to gather data and monitor progress. Details regarding the timing of enrollment, interventions, assessments, monitoring, and follow-ups were represented in Table 1, which offers an overview of the study's timeline. The study was retrospectively registered in the Iranian Registry of Clinical Trials (IRCTID: IRCT20210217050393N4). The study was approved by the Research Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (reference approval number: IR.MUMS.MEDICAL.REC.1402.112) for design and development of an anti-inflammatory an oral nutrition supplement (ONS) formula and its effects on inflammatory markers, antioxidants status, and clinical outcomes in critically ill patients admitted to the intensive care units.

Our hypothesis was that an anti-inflammatory formula for ONS in critically ill patients, in addition to their common treatments were shown better outcomes compared to those in the control group.

Table 1: Schedule of enrollment, intervention, and assessment of the clinical trial.

Timeline	Study period						
	Enrolment	Allocation	Post-allocation			Follow-up	
			Day 0	Day 7	Day 14		
Enrollment	*					28 days after intervention	60 days after intervention
Eligibility screen	*						
Informed consent	*						
Demographic data	*						
Blood culture	*						
BIA analyses	*						
Allocation		*					
Interventions							
Group 1: Anti-inflammatory ONS			←	—	→		
Group 2: Standard ONS			←	—	→		
Primary outcomes			*	*	*		
Secondary outcomes			*	*	*		
Follow up						*	*

BIA: Bioimpedance analysis, ONS: oral nutritional supplement.

Various clinical outcomes and disease severity parameters, such as Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology II (SAPS II) score, modified Nutrition Risk in the Critically Ill (mNUTRIC) score, inflammatory factors [High-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR)], and antioxidant factors (malondialdehyde (MDA), total antioxidant capacity (TAC)) would be predicted to demonstrate improvement in the treatment groups in comparison to the control group.

The specific aims were received to compare various variables in two groups of critically ill patients receiving "standard ONS formula" and "anti-inflammatory ONS formula" as follows: 1) Comparing inflammatory factors (hs-CRP, ESR); 2) antioxidant factors (MDA, TAC); 3) fasting blood glucose level (FBG); 4) lipid levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C); 5) liver enzyme levels of alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP); 6) mid-arm circumference (MAC); disease severity scores such as 7) APACHE II score, 8) SOFA score, 9) SAPS II score; nutritional status of patients using 10) mNUTRIC score; nutritional status of patients using changes in 11) body composition (fat mass and fat-free mass) measured by Bioelectrical Impedance Analysis (BIA); 12) gastrointestinal complications (diarrhea, constipation, distension, etc.); 13) 28-day and 60-day mortality; 14) ICU and hospital length of stay in the intensive care unit; and the 15) healing status of burn wounds.

This was a two-phase, randomized, double-blind clinical trial. It was conducted at the Imam Reza Hospital at Mashhad University of Medical Sciences of Iran, assessed the effects of the daily implementation of anti-inflammatory ONS formula in critically ill patients. Totally, 74 critically ill sepsis and ARDS patients admitted to ICUs of Imam Reza Hospital were enrolled based on inclusion and exclusion criteria. Based on the findings of the previous study (18) and the mean and standard deviation of hs-CRP in the control and intervention groups on day 7, the sample size was determined. Therefore, the sample size for each group was determined to be 37 individuals, considering a 95% confidence interval (95% CI) and 80% test power.

Block randomization with blocks of size 4 was used, where the random list was generated from the website of https://www.sealedenvelope.com/. Patients were allocated to two groups of control and intervention, using sealed envelopes with randomization through the block randomization method. This was done in blocks of size 4, which were divided into four states, and each state was randomly selected from the sealed envelopes, with 4 patients in the control and intervention groups assigned based on the selected state of the sealed envelope. This process was continued until all participants were allocated to control and intervention groups.

After obtaining the formulation containing vitamins, minerals, and nutrients from the pharmaceutical team and professors of the pharmaceutics department, and then adding them to the standard entrameal formula of PNC to prepare the intervention group formula, both the control and intervention formulas were transferred to the hospital. In the hospital catering (aseptic gavage room), after preparing the gavage solution in uniform bottles, it was numbered and coded, transferred to the ICU, handed over to the respective nurse, and administered to patients who were randomly be allocated to the control and intervention groups based on the required calorie and volume requested by the treating physician and nutrition expert. Since physicians, patients, and statistical analyzer were blinded to the numbering and coding of the gavage solutions, and due to the similar physical, tissue, and organoleptic characteristics of the gavage solutions of both groups, the blinding process were carried out with great precision.

To achieve the study objectives, objectives 1 to 11 and objectives 14 and 15 are assessed for normality using the Shapiro-Wilk test. If the data distribution was normal, the t-test was used, otherwise the Mann-Whitney test was utilized. For objectives 12 and 13, the comparison of proportions test was applied. Furthermore, to control for the variable effect of nothing by mouth (Nil per os: NPO), the analysis of covariance (ANCOVA) test and Mantel-Haenszel Chi-Square test are employed. Additionally, to control for the variable effect of diarrhea, preferably categorical analyses are undertaken.

The inclusion criteria for the study require that adult participants newly admitted to the intensive care unit to be aged 18 years or older with proper gastrointestinal tract function. Additionally, patients should meet the criteria for enteral nutrition to be eligible for inclusion. Non-entry criteria for the study include the impossibility of enteral feeding within the first 48 hours of admission, patients unable to receive enteral nutrition in the future due to medical conditions, and those with a history of heart failure or thyroid disease. Additionally, patients hospitalized in the intensive care unit for less than 96 hours, those expected to die within 12 hours of admission, and those receiving parenteral nutritional support via

Total Parenteral Nutrition (TPN) were excluded. Further exclusions included patients with a history of underlying diseases such as congenital and immune disorders, kidney and liver failure, pancreatitis, or those undergoing dialysis, and the lack of consent from the patient or their legal guardian.

Exclusion criteria for the study included patients receiving corticosteroid medications and those who experience frequent and refractory feeding intolerances, making enteral nutrition unsuitable. Additionally, patients with infectious processes such as diffuse intravascular coagulation (DIC) and any inflammatory conditions interfering with the intervention process were excluded. The study was evaluating variables such as demographic factors, disease severity assessment, anthropometric measurements, inflammatory and antioxidant markers, nutritional assessments, body composition factors, feeding intolerance, and mortality at 28 and 60 days.

The intervention group was received 500 mL of anti-inflammatory ONS formula (daily) and the control group was received 500 mL of standard ONS formula (daily). The outcome used to calculate the sample size was based on hs-CRP in the control and intervention groups. The study outcomes were demonstrated in Table 2. In this study, 74 adult patients aged more than 18 years, diagnosed with conditions such as surgery, sepsis, ARDS or severe stroke were enrolled within 24-48 hours of being admitted to the general ICUs. Patients are selected based on specific inclusion and exclusion criteria. They are randomly assigned into two groups, considering factors such as age, gender, type of lesion, severity of the disease, and Glasgow Coma Scale (GCS) score. The sampling method was non-probability, purposive sampling, adhering to the study's inclusion and exclusion criteria.

In a Phase I/Pharmacological Phase after preparing the standard entrameal formula by Karen PNC company considering the coefficients of the DII index and the levels of Upper Limit (UL) and RDA of the ingredients used in this formula, an increased ratio of certain vitamins and minerals (vitamins A, D3, E, C, B1, B2, B3, B6, B9, and minerals magnesium, zinc, and selenium, curcumin, carnitine, propolis, and saffron) with negative DII coefficients and anti-inflammatory properties are added to the standard entrameal formula, creating a new formula with a lower inflammatory index for use in the intervention group. The new formulation is based on a previous phase study formulation (18). The previous phase formulation was patented with the Iran national patent number (102502) and international classification (A61K 31/015, A23L 1/29, A23L 1/302, A61P 3/02, A01N 43/04) (https://ipm.ssaa.ir/Search-Result?page=1&DecNo=139950140003002103&RN=102502) and had significant positive clinical results in last pilot phase (18).

This new formulation is three times richer in most vitamins and minerals compared to the previous formulation. Also, several new substances such as propolis and L-carnitine are added based on the amounts that are found to be safe in these patients, according to the text review conducted (20, 21), and as a substitute for turmeric in the previous study, the active ingredient curcumin was added to the new formula; while the related properties of curcumin were previously described (22-25). It is worth

Table 2: Study outcomes.

Primary outcomes
Inflammatory factors (hs-CRP, ESR)
Antioxidant factors (MDA, SOD, TAC).
Mortality (28- and 60- day mortality)
Length of stay (ICU LOS and hospital LOS)
Secondary outcomes
BG level
Lipid profile levels (HDL-c, LDL-c, TC, TG).
Liver enzyme levels (ALT, AST, ALP).
MAC
APACHE II, SOFA, SAPS II, mNUTRIC Score.
Body composition and FFM
Gastrointestinal complications (diarrhea, constipation, distension, etc.)

ALP: Alkaline phosphatase, ALT: Alanine transaminase, APACHE II: Disease severity is assessed by indices, AST: Aspartate transaminase, BG: Blood glucose, FFM: Fat-Free Mass, ESR: Erythrocyte sedimentation rate, FM: Fat Mass, HDL-C: High-density lipoprotein cholesterol, hs-CRP: High sensitive-C-reactive protein, ICU: Intensive Care Unit, LDL-C: Low-density lipoprotein cholesterol, LOS: Length of stay, MAC: Mid-arm circumference, MDA: Malondialdehyde, mNUTRIC: modified Nutrition Risk in the Critically Ill, SAPS II: Simplified Acute Physiology II, SOD: Superoxide dismutase, SOFA: Sequential Organ Failure Assessment, TAC: Total antioxidant capacity, TC: Total cholesterol, TG: Triglycerides

mentioning that the quantities of the new formulation are designed based on the daily needs of patients and considering the intake from other sources to ensure that the intake of essential nutrients does not exceed the UL and is not toxic. It is important to note that due to the process of registering the formulation with the intellectual property organization and the patent office in Iran, disclosing the details of the formulation at this stage is not possible. However, the formulation details, along with the main findings of the study, will be published in future.

Initially, a sample premix with specified doses of vitamins, minerals, and desired nutrients to be added to the desired amounts of Standard Entrameal formula prepared in the pharmaceutical laboratory of the Faculty of Pharmacy, Mashhad University of Medical Sciences, by a team of nutrition and pharmaceutics experts. Subsequently, the final mix of standard entrameal powder and the sample premix went through various mixing processes, including conical and geometric mixers, as well as an industrial mixer, in a pharmaceutical company.

In Phase II/ Intervention Phase; data were collected through laboratory methods, anthropometric evaluation, Bioelectrical Impedance Analysis (BIA), and observational tools. Demographic information, including age, gender, diagnosis, personal characteristics, and medical and drug history, were obtained from comprehensive hospital management software. Given the critical condition of patients in the ICU, informed consent was obtained from the patient's legal representative if the patient was unable to provide consent due to unconsciousness. Nutrition support was provided with energy equivalent to 80-100% of the patient's estimated energy requirement, calculated as 25 kilocalories per kilogram of the patient's weight (26).

Two treatment interventions were used in this study. The control group received the standard ONS formula as two times gavage meals, while the intervention group received an anti-inflammatory formula with a low inflammatory profile delivered in the same way as the control group. The specific amount of formula required for each patient in both groups, enteral nutrition support was begun after resuscitation and stabilization of hemodynamic status within 24-48 hours of hospitalization. The nutritional feeding was administered at equal intervals of 3 hours, five times in 24 hours, via hospital gavage, and two times with a bolus of 500 mL ONS. The intervention period was last for 14 days for each patient, after which both groups were returned to standard enteral nutrition protocols of the hospital. Blood samples were collected from patients in both groups after the last nighttime gavage (before the first meal in the morning) at baseline, day 7, and day 14. This consistent timing ensured that sample collection was comparable and uniform across all study groups.

There were no dangerous or life-threatening complications. However, there was a possibility of gastrointestinal symptoms such as diarrhea and distension as with other enteral nutrition formulas, and the occurrence of these symptoms was rare. The low-DII is likely to be associated with fewer symptoms. However, at any stage of the study, the team of nutritionists were monitored the patients and if any symptoms occur, they take the necessary measures (such as interrupting and stopping the intervention) also in case of digestive intolerance, which was very rare, the patient was excluded from the study. At any stage of the study, if there are any questions from the patient or his guardian, the researchers were answered. All stages of the study were completed in a way that ensured that all patients' information remained completely confidential.

Participating in the study was completely voluntary and the patient's guardians were free to refuse to participate in the study or to withdraw from the study at any time without any change in the behavior of the treating doctor or in the way of treating and caring for my illness. In this study, the height of patients was calculated based on Ulna Length and their ideal weight was determined based on their height due to lack of facilities, budget constraints, and patient conditions. The body mass index (BMI) of patients was calculated using the height obtained from the Ulna Length method and their ideal weight as follows: BMI=(Height (m)^2/ Weight (kg). For MAC, measurements were taken in centimeters at the midpoint between the acromion process of the shoulder and the olecranon process at the tip of the elbow.

Regarding bioimpedance analysis (BIA), the InBody S10 (InBody®, Seoul, Korea) was used to assess body composition, including Fat Mass (FM) and Fat-Free Mass (FFM). The BIA method calculates body composition based on the resistance value (impedance) that arises from differences in electrical conductivity due to the biological characteristics of each tissue. The amount of water and electrolytes in the body determines its electrical conductivity. Since the water content of fat tissue is relatively lower than that of other tissues, an increase in fat content leads to a decrease in electrical conductivity (27).

For biochemical assessments, 10 mL of venous blood was collected from each patient before their first meal in the morning. The serum was separated by centrifugation at 3000 rpm for 10 minutes and then stored at -70°C until further analysis. Serum levels of hs-CRP, superoxide dismutase (SOD), and TAC

were measured using a commercial ELISA kit. The spectrophotometric method was used to determine serum MDA using the thiobarbituric acid reactive substance method. Additionally, serum levels of TG, TC, and HDL-C were measured enzymatically. LDL-C was calculated using the Friedewald formula as follows: LDL-C=(Total cholesterol-HDL-C)–(TG/5).

The severity of the disease was assessed using the APACHE II score, SOFA score, SAPS II, and mNUTRIC score. To assess the nutritional status of patients, the NUTRIC score and MAC were used as indicators. Patient height was calculated based on Ulna Length, and their ideal weight was calculated based on their height. To calculate BMI based on patients height obtained from the Ulna Length method and ideal weight was used. The formula used was be height (m) squared divided by weight (kg) which equals BMI. Regarding feeding intolerance, the two groups received different nutrition plans tailored to their specific energy needs, determined with the help of a nutrition specialist and consultant. If the standard protocol was not effective due to high residual and resistance, special attention was given to the use of prokinetic drugs.

The nutrition consultant and nursing team monitored the patient's gastrointestinal tolerance, abdominal softness, bowel movements, and at least once-a-day defecation before each meal. Blood sugar control followed the hospital's usual special care section routine (less than 180 milligrams per deciliter), and the patient was not served a meal between 12 midnight and 6 am. For 28- and 60- day mortality assessments; mortality was a standard outcome measure reported in clinical studies in mechanically ventilated critically ill patients with ARDS and sepsis. The patient's mortality was evaluated on day 28 and day 60. In addition to mortality, ICU and hospital length of stay were recorded.

Discussion

Inflammation is vital to mounting an immune response that occurs when the body is affected by factors like trauma, surgery, radiation, and infections from bacteria or viruses (28-30). This response involves cytokines, a diverse group of small soluble proteins that provide inflammatory responses (31, 32). Acute inflammation, a natural immune response to trauma, injury, or burns, involves increased transfer of plasma, leukocytes, antibodies, and complements to peripheral tissues to restore normal function and metabolic stability (28, 31). However, unresolved triggers can lead to systemic inflammatory response syndrome (SIRS) (5).

SIRS is characterized by widespread inflammation affecting all organs due to non-infectious stressors such as burns, trauma, or infectious origins. SIRS causes dysfunctional organ responses as the body defensively responds to stressors (33), resulting in the overproduction of inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8. In cases where infection is the cause, SIRS progresses to sepsis, a severe systemic response that requires special treatment and care (5). Despite advances in treatment strategies, sepsis remains a critical challenge in ICU patient management, with high morbidity and mortality rates persisting (5). Contemporary evidence emphasizes that appropriate timing, dose, and composition of nutrition support are fundamental components of intensive care management (34).

Nutritional interventions play a crucial role in modulating inflammation, oxidative stress, and immune function. Key nutrients such as amino acids, antioxidant vitamins, minerals like selenium, n3 long-chain fatty acids, and nucleotides have demonstrated efficacy in surgical, injured, and critically ill patients (15, 16). Recent evidences suggested that targeted nutritional interventions may influence inflammatory resolution, oxidative stress, immune dysfunction, and metabolic recovery throughout the different phases of critical illness (6).

While immunonutrition formulations containing antioxidants, arginine, glutamine, vitamins C and E, and n3 fatty acids have shown benefits in surgical settings (15, 16, 35), their effectiveness in critically ill patients remains controversial and requires further studies with larger sample sizes (35, 36). Recent evidences support a more personalized approach to immunonutrition, considering the phase of illness, inflammatory burden, and metabolic response rather than applying uniform nutritional strategies to all critically ill patients (37). Given the significant impact of diet on inflammatory processes, antioxidant levels, lipid profiles, and intestinal microbiota balance, the DII was developed to reduce inflammatory markers in ICU patients.

Conclusion

This research was tested a formula with a low inflammatory index that contains essential vitamins, minerals, and nutrients with antioxidant properties that also are likely to improve inflammatory responses, as reflected by inflammatory cytokines and metabolic biomarkers including liver enzymes, lipid factors, and blood sugar. It was expected to see the impact on clinical outcomes such as disease severity in critically ill patients through its own antioxidant and anti-inflammatory properties in various processes.

Acknowledgement

We thank the Mashhad University of Medical

Sciences, patients, their families, Karen Pharmaceutical and Supplement Distribution Company, and all those who helped in this study.

Funding

This study was funded by a grant from the Mashhad University of Medical Sciences.

Authors' Contribution

SJ, MGM, HT, ABM, AS and RR contributed to the conception or design. SJ and MH drafted the protocol and all co-authors contributed to the final version. SJ, RR, JRH, MRA prepared the anti-inflammatory formula. SJ, MH, KKN and SM collected samples at ICU while HT contributed to acquisition, analysis, or interpretation.SJ, RR, MGM, ABM, and AS critically revised the manuscript and RR, HT, and AS gave final approval. RR also agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of Interest

Dr. James R. Hébert owns a controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smartphone applications for patient counseling and dietary intervention in clinical settings. The subject matter of this paper will not have any direct bearing on that work or has that activity exerted any influence on this project.

References

1 Lat TI, McGraw MK, White HD. Gender Differences in Critical Illness and Critical Care Research. *Clin Chest Med*. 2021;42:543-55. DOI: 10.1016/j.ccm.2021.04.012. PMID: 34353458.

2 Santacroce E, D'Angerio M, Ciobanu AL, et al. Advances and Challenges in Sepsis Management: Modern Tools and Future Directions. *Cells*. 2024;13:439. DOI: 10.3390/cells13050439. PMID: 38474403.

3 Lashkarizadeh MM, Ghaedi A, Abolghasemi H, et al. Comparison of gauze packing, sponge-based, and hemostatic surgicel wound stasis dressings to treat hemorrhages from grade IV liver injuries: An experimental study. *Heliyon*. 2024;10:e39894. DOI: 10.1016/j.heliyon.2024.e39894. PMID: 39539973.

4 Moradi AM, Aj O, Paydar S, et al. The effect of blood loss in the presence and absence of severe tissue damage on hemodynamic and metabolic parameters in experimental rat model. *Emerg (Tehran)*. 2014;3:150-154. PMID: 26495405.

5 Mahan LK, Raymond JL. Krause's food & the nutrition care process-e-book: Elsevier Health Sciences; 2016.

6 Rousseau A-F, Martindale R. Nutritional and metabolic modulation of inflammation in critically ill patients: a narrative review of rationale, evidence and grey areas. *Ann Intensive Care*. 2024;14:121. DOI: 10.1186/s13613-024-01350-x. PMID: 39088114.

7 Mehrabani D, Vahedi M, Eftekhari MH, et al. Food avoidance in patients with ulcerative colitis: a review. *Int J Nutr Sci*. 2018;2:189-95.

8 Moatari-Kazeruni M, Daryanoosh F, Mehrabani D. The Effect Of 8 Weeks Anaerobic Exercise And Omega 3 On Inflammatory Factors In Male Rat. *J Sport Physiol*. 2012;15:97-108.

9 Hegazi RA, Wischmeyer PE. Clinical review: optimizing enteral nutrition for critically ill patients-a simple data-driven formula. *Crit Care*. 2011;15:234. DOI: 10.1186/cc10430. PMID: 22136305.

10 Calder PC. Immunonutrition. *BMJ*. 2003;327:117-8. DOI: 10.1136/bmj.327.7407.117. PMID: 12869428.

11 Calder PC. n− 3 Fatty acids, inflammation, and immunity—Relevance to postsurgical and critically III patients. *Lipids*. 2004;39:1147-61. DOI: 10.1007/s11745-004-1342-z. PMID: 15736910.

12 McCarthy MS, Martindale RG. Immunonutrition in Critical Illness: What Is the Role? *Nutr Clin Pract*. 2018;33:348-58. DOI: 10.1002/ncp.10102. PMID: 29878555.

13 Lopez-Delgado JC, Grau-Carmona T, Trujillano-Cabello J, et al. The Effect of Enteral Immunonutrition in the Intensive Care Unit: Does It Impact on Outcomes? *Nutrients*. 2022;14:1904. DOI: 10.3390/nu14091904. PMID: 35565870.

14 Abunnaja S, Cuviello A, Sanchez JA. Enteral and parenteral nutrition in the perioperative period: state of the art. *Nutrients*. 2013;5:608-23. DOI: 10.3390/nu5020608. PMID: 23429491.

15 Klek S, Sierzega M, Szybinski P, et al. Perioperative nutrition in malnourished surgical cancer patients–a prospective, randomized, controlled clinical trial. *Clin Nutr*. 2011;30:708-13. DOI: 10.1016/j.clnu.2011.07.007. PMID: 21820770.

16 Marano L, Porfidia R, Pezzella M, et al. Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. *Ann Surg Oncol*. 2013;20:3912-8. DOI: 10.1245/s10434-013-3088-1. PMID: 23838912.

17 Shivappa N, Steck SE, Hurley TG, et al.

Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* 2014;17:1689-96. DOI: 10.1017/S1368980013002115. PMID: 23941862.

18 Jandari S, Rezvani R, Yousefian S, et al. The effect of low dietary inflammatory index score formula on inflammatory, metabolic, and clinical outcomes in critically ill traumatic brain injury patients: A single-blind randomized controlled pilot study. *Food Sci Nutr.* 2023;11:3365-75. DOI: 10.1002/fsn3.3326. PMID: 37324871.

19 Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* 2013;346:e7586. DOI: 10.1136/bmj.e7586. PMID: 23303884.

20 Pahlavani N, Sedaghat A, Ferns GA, et al. The Effects of Melatonin and Propolis on Markers of Inflammation, Oxidative Stress, Clinical Outcomes, and Survival Rate in Patients with Primary Sepsis Hospitalized in Intensive Care Unit: A Randomized Clinical Trial. *Res Square.* 2020. DOI: 10.21203/rs.3.rs-56718/v1.

21 Yahyapoor F, Sedaghat A, Feizi A, et al. The effects of l-Carnitine supplementation on inflammatory markers, clinical status, and 28 days mortality in critically ill patients: A double-blind, randomized, placebo-controlled trial. *Clin Nutr ESPEN.* 2022;49:61-7. DOI: 10.1016/j.clnesp.2022.04.001. PMID: 35623869.

22 Zahedi H, Hosseinzadeh-Attar MJ, Shadnoush M, et al. Effects of curcuminoids on inflammatory and oxidative stress biomarkers and clinical outcomes in critically ill patients: A randomized double-blind placebo-controlled trial. *Phytother Res.* 2021;35:4605-15. DOI: 10.1002/ptr.7179. PMID: 34080237.

23 Mehrabani D, Farjam M, Geramizadeh B, et al. The healing effect of curcumin on burn wounds in rat. *World J Plast Surg.* 2015;4:29-35. PMID: 25606474.

24 Panjehshahin MR, Owji AA, Mehrabani D, et al. Effect Of Curcumin On Cholesterol Gall-Stone Induction In Rats. *J Appl Anim Res*. 2003;23:75-80. DOI: 10.1080/09712119.2003.9706771.

25 Rabbani-Haghighi N, Naghsh N, Mehrabani D. the protective effect of curcuma longa in thioacetamide-induced hepatic injury in rat. *Global J Pharmacol*. 2013;7:203-207. DOI: 10.5829/idosi.gjp.2013.7.2.74203.

26 Kreymann K, Berger M, Deutz Ne, et al. ESPEN guidelines on enteral nutrition: intensive care. *Clin Nutr*. 2006;25:210-23. DOI: 10.1016/j.clnu.2006.01.021. PMID: 16697087.

27 Oh HJ, An JN, Oh S, et al. VolumE maNagement Under body composition monitoring in critically ill patientS on CRRT: study protocol for a randomized controlled trial (VENUS trial). *Trials*. 2018;19:681. DOI: 10.1186/s13063-018-3056-y. PMID: 30541593.

28 Rabb H, Griffin MD, McKay DB, et al. Inflammation in AKI: current understanding, key questions, and knowledge gaps. *J Am Soc Nephrol*. 2016;27:371-9. DOI: 10.1681/ASN.2015030261. PMID: 26561643.

29 Alizadeh H, Daryanoosh F, Mehrabani D. Evaluating Inflammatory Index Changes And Muscle Injuries In Male Mice After 8 Weeks Of Aerobic Exercise And Omega-3 Consumption. *J Sport Biosci*. 2012;10:77-94. DOI: 10.22059/jsb.2012.21999.

30 Malekzadeh S, Edalatmanesh MA, Mehrabani D, et al. Dental Pulp Stem Cells Transplantation Improves Passive Avoidance Memory and Neuroinflammation in Trimethyltin-Induced Alzheimer's Disease Rat Model. *Galen Med J*. 2021;10:e2254. DOI: 10.31661/gmj.v10i.2254.

31 Leng SX, McElhaney JE, Walston JD, et al. ELISA and multiplex technologies for cytokine measurement in inflammation and aging research. *J Gerontol A Biol Sci Med Sci*. 2008;63:879-84. DOI: 10.1093/gerona/63.8.879. PMID: 18772478.

32 Goudarzi Z, Hoseini SE, Mehrabani D, et al. Change in blood chemistry, pro-inflammatory cytokines, and apoptotic genes following methamphetamine use in experimental rats. *Periódico Tchê Química*. 2020;17:1147-1159.

33 Marik PE, Taeb AM. SIRS, qSOFA and new sepsis definition. *J Thorac Dis*. 2017;9:943-5. DOI: 10.21037/jtd.2017.03.125. PMID: 28523143.

34 Reignier J, Rice TW, Arabi YM, et al. Nutritional Support in the ICU. *BMJ*. 2025;388:e077979. DOI: 10.1136/bmj-2023-077979. PMID: 39746713.

35 Barker LA, Gray C, Wilson L, et al. Preoperative immunonutrition and its effect on postoperative outcomes in well-nourished and malnourished gastrointestinal surgery patients: A randomised controlled trial. *Eur J Clin Nutr.* 2015;67:802-7. DOI: 10.1038/ejcn.2013.117. PMID: 23801093.

36 Falewee M, Schilf A, Boufflers E, et al. Reduced infections with perioperative immunonutrition in head and neck cancer: exploratory results of a multicenter, prospective, randomized, double-blind study. *Clin Nutr.* 2014;33:776-84. DOI: 10.1016/j.clnu.2013.10.006. PMID: 24182765.

37 Yeh DD. Fueling recovery: evidence-based ICU nutrition and immunonutrition strategies in 2026. *Trauma Surg Acute Care Open*. 2026;11:e002284. DOI: 10.1136/tsaco-2026-002284. PMID: 42094750.