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Impact of immunonutrient use on clinical outcomes in critical patients: a systematic review of clinical trials

Impacto do uso de imunonutrientes no desfecho clínico de pacientes críticos: uma revisão sistemática de estudos clínicos

Abstract

Objective: To describe the outcomes regarding the impact of immunonutrients on mortality rates, length of hospitalization, duration of Intensive Care Unit (ICU) stays, and the incidence of infections in adult and elderly critical patients. **Method:** An integrative literature review was conducted using the PubMed, LILACS, SciELO, Medline, and Google Scholar databases, using the descriptors: ("immunomodulation" OR "immunonutrients") AND ("fatty acids, Omega-3" OR "eicosapentaenoic Acid") AND ("glutamine") AND ("critical illness" OR "critical illnesses" OR "critically ill"), without language restrictions. The search encompassed studies that were published between 2012 and 2022. **Results:** Fifteen publications were identified in the conducted searches, of which eleven met all the established criteria at the outset of the study. Although some studies involving individuals supplemented with immunomodulatory formulas demonstrated improvements in ICU length of stay, a reduced incidence of sepsis and septic shock, and a lower infection rate, most of the evaluated studies did not reveal significant differences between the supplemented groups and the control groups or did not yield statistically significant outcomes. **Conclusion:** The management of care for critical patients necessitates a cautious and individualized approach, underpinned by scientific evidence. The analysis of clinical studies forming part of this research revealed an absence of statistically significant results pertaining to the practice of immunomodulation utilization in critical patients with respect to effects on mortality, ICU length of stay, total hospitalization, and the incidence of infections. Further studies are required to validate the genuine benefits of adopting this approach.

Keywords: Immunomodulation. Critical illness. Outcome Assessment Health Care.

Resumo

Objetivo: Descrever os resultados da influência de imunonutrientes na taxa de mortalidade, tempo de internação, tempo de permanência na Unidade de Terapia Intensiva (UTI) e incidência de infecções em pacientes críticos adultos e idosos. **Método:** Revisão integrativa da literatura realizada nas bases de dados PubMed, LILACS, SciELO, Medline e Google Scholar, usando os descritores: ("immunomodulation" OR "immunonutrients") AND ("fattyAcids, Omega-3" OR "eicosapentaenoic Acid") AND ("glutamine") AND ("criticalillness" OR "criticalillnesses" OR "criticallyill"), sem restrição de idioma, com pesquisas realizadas no período de 2012 a 2022. **Resultados:** Nas buscas realizadas, foram encontradas 15 publicações, das quais 11 atenderam a todos os critérios estabelecidos ao início do estudo. Apesar de alguns estudos com indivíduos suplementados com fórmulas imunomoduladoras demonstrarem melhora no tempo de internação de UTI, redução de ocorrência de sepse e choque séptico, e redução de taxa de infecções, em sua maioria os estudos avaliados não mostraram

diferença entre os grupos suplementados e os grupos controle, ou não apresentaram resultados estatisticamente significativos. **Conclusão:** O manejo do cuidado em pacientes críticos deve ser cuidadoso e individualizado, sendo imprescindível que a conduta clínica tenha como base evidências científicas. No presente estudo, a análise dos estudos clínicos que compuseram esta pesquisa verificou que os efeitos da imunomodulação na mortalidade, tempo de internação na UTI e hospitalização total e incidência de infecções, demonstrou ausência de resultados significativos para a prática de uso de imunonutrientes em pacientes críticos, sendo necessário realizar outros estudos para comprovar os reais benefícios da adoção dessa conduta.

Palavras-chaves: Imunomodulação. Estado crítico. Avaliação de Resultados em Cuidados de Saúde.

INTRODUCTION

The critically ill patient is defined as one who is at imminent risk of losing life or organ/system function. This state is characterized by a condition of metabolic stress and pronounced protein catabolism. It is accompanied by significant metabolic changes that increase nutritional requirements, resulting in a catabolic state and negative nitrogen balance.^{1,2}

During this process, an inflammatory state occurs characterized by an increase in the plasma concentration of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukins 6 (IL-6), and interleukin 8 (IL-8), along with a decrease in regulatory cytokines, such as interferon γ and interleukins 1 (IL-1), 2 (IL-2), and 10 (IL-10). There is also a decrease in the bactericidal potential of neutrophils, excessive activation of the monocyte/macrophage system, and reduced lymphocyte proliferation.²

As a result of these changes, protein malnutrition and the pro-inflammatory state alter the immune system, transforming the inflammatory response and impairing immune mechanisms, including tissue synthesis, regeneration, infection control, and changes in the existing microflora ecology, leading to alterations in mucosal structure. Consequently, patients in these conditions have a higher likelihood of developing infectious complications, severe tissue depletion, and higher rates of mortality, prolonged hospitalization, and morbidity.³

Among the cellular components involved in immunity, the T cell-dependent immune system plays a significant role in wound healing. T lymphocyte activation promotes the recruitment, expansion, and stimulation of fibroblasts, which are primarily responsible for intestinal barrier function, tissue oxygenation, and wound healing. Therefore, some research has shown that immune system modulation can bring benefits such as reducing inflammation, mitigating the acute-phase response, and enhancing T cell activity, resulting in a lower incidence of infections.³

It can be defined as the provision of nutrients in amounts greater than habitual dietary intake that modulate the functioning of the immune system. Among them, there is glutamine and polyunsaturated fatty acids omega-3 (PUFA) – composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – which can function as anti-inflammatory agents, nourish immune cells, and optimize intestinal permeability.⁴

As one of the main substances involved in the metabolism of intestinal cells is glutamine (Gln), the primary energy source for enterocytes and one of the most abundant amino acids in muscle tissues, blood plasma, and other tissues. Among its various functions, Gln promotes increased antioxidant activity in the body, prevents bacterial translocation by protecting the intestinal mucosa, and increases the production of proteins that reduce inflammation. Moreover, it is used as an energy substrate for lymphocytes and can support the production and function of macrophages and monocytes in the proper restoration of the immune system.⁵

In a body without metabolic disorders analyzed from a microbiological perspective, when gram-negative bacteria in the intestine favor homeostasis. However, in critical conditions, they can promote infections in the host. In a healthy individual, the immune system and the intestinal mucosa act as barriers against bacteria and other microorganisms, a situation that does not occur in critically ill patients, where changes in mucosal structure make it more susceptible to the passage of pathogenic microorganisms, serving as an entry point for other body systems (lymphatic, portal, and others). In this condition, the risk of infection, sepsis, mortality rate, prolonged hospitalization, and increased intestinal permeability are elevated due to immune system suppression and oxidative stress.⁵

Therefore, in a catabolic state, Gln can experience a reduction in its plasma concentration of about 50% due to intense immune activity, resulting in an inability to meet the body's demand and making it a conditionally essential amino acid. This deficiency leads to reduced expression of surface activation proteins, reduced cytokine production, and induction of immune cell apoptosis. In critically ill patients, there is a high synthesis of pro-inflammatory cytokines, resulting in increased Reactive Oxygen Species (ROS) levels. This dysregulation leads to an intense inflammatory response and attacks on the cell membrane through lipid peroxidation.⁵⁻⁷

Thus, the role of glutamine in critical conditions becomes important as it acts as an immunonutrient with the ability to intervene in the immune response through anti-inflammatory action, reduced proteolysis, activation of proteins responsible for cell differentiation and proliferation, promoting maintenance of the intestinal barrier, reducing bacterial translocation, and endotoxemia.^{5,8}

Regarding EPA and DHA, which constitute PUFAs, these have properties that reduce the production of pro-inflammatory cytokines and lipid mediators, regulate the expression of nuclear transcription factors (nuclear factor kappa B), and activity of nuclear receptors, as well as serving as precursors to mechanisms that alleviate inflammation. In nutritional therapy, one of the lipid emulsions used is fish oil, a significant source of PUFAs, which play immunomodulatory and anti-inflammatory roles⁹.

In addition, these fatty acids can influence inflammation and immune function by reducing the production of eicosanoids derived from Arachidonic Acid (AA) and increasing the formation of mediators that regulate the inflammatory state (pro-resolving mediators) derived from EPA and DHA. In this regard, cohort studies have found inverse associations when analyzing dietary intake or blood concentrations of DHA and EPA with serum levels of inflammatory markers such as acute-phase proteins, cytokines, and adhesion molecules. Other studies have reported the ability of these nutrients to defend against infections, such as the reduction of respiratory infections in children who received EPA and DHA supplementation or who had them added to the milk offered.¹⁰⁻¹²

In addition, studies have found a tendency to reduce the length of stay in the Intensive Care Unit (ICU) and improve clinical outcomes in patients with acute respiratory distress syndrome (ARDS) who received immunomodulatory nutritional therapy containing EPA and DHA combined with Gamma-Linolenic Acid (GLA) and other antioxidants. Other research has shown a trend towards reduced mortality rates and days of Mechanical Ventilation (MV) in critically ill patients receiving lipid emulsions containing fish oil.^{13,14} Furthermore, in a meta-analysis conducted by Palmer et al.,¹⁵ a reduction in total hospitalization time was found in critically ill patients supplemented with omega-3 fatty acids via parenteral administration.

Therefore, as these nutrients act on the immune system's functioning and have potential beneficial effects as immunomodulators, it is essential to understand the results of these nutrients in situations where the immune system is compromised, such as in critically ill patients. This study aims to describe the outcomes of immunonutrient use on mortality, total hospitalization time, ICU stay duration, and incidence of infections in critically ill adult patients by researching studies on immunonutrient supplementation via enteral or parenteral route in critical illness between 2002 and 2022 in databases.

METHOD

This work is based on a review that aims to gather and condense information from relevant studies on a specific topic, providing a scientific basis for practice. It enables evidence-based clinical practice and

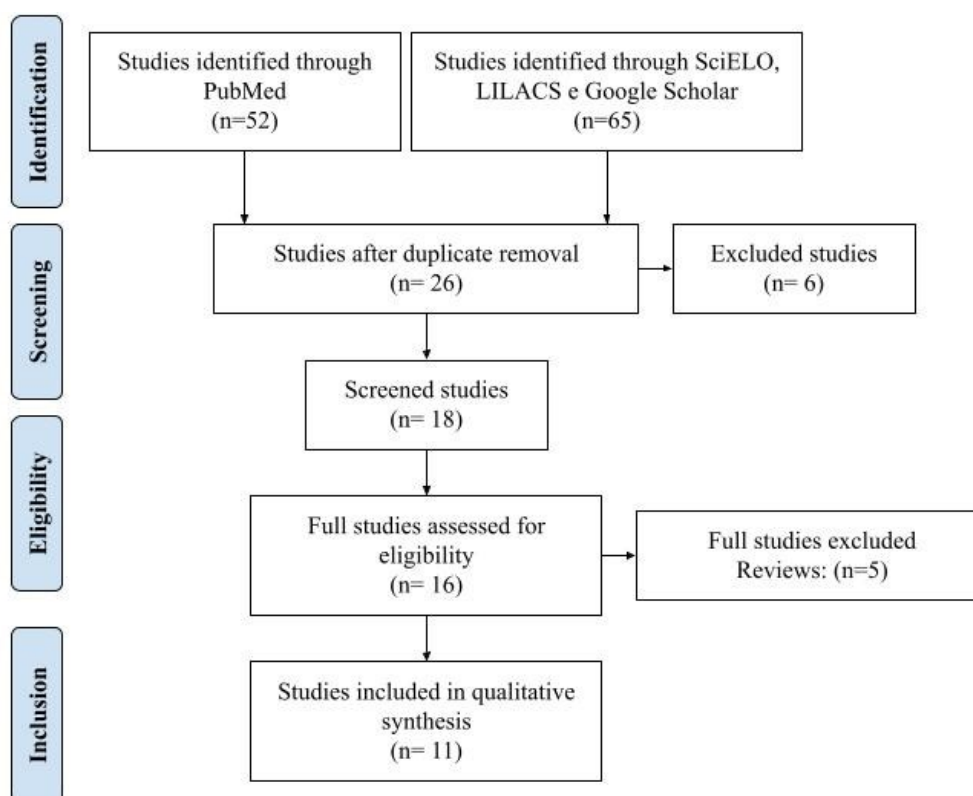
highlights knowledge gaps that need to be clarified through further research. Therefore, the development of this research was guided by the following steps: identification of the topic, literature search, extraction and analysis of results, and data presentation.¹⁶⁻¹⁸

This is a review produced from clinical trials using Mesh/DeCS descriptors, according to the Health Sciences Descriptors (DeCS), containing the terms ("immunomodulation" OR "immunonutrients") AND ("fatty acids, Omega-3" OR "eicosapentaenoic Acid") AND ("glutamine") AND ("critical illness" OR "critical illnesses" OR "critically ill"), with no language restrictions, conducting searches from 2012 to 2022. To search for studies, queries were performed in the electronic databases PubMed, Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (Medline), and Google Scholar.

Only original studies that met the following inclusion criteria were included: a) study design: randomized clinical trials, controlled trials, b) population: adult critical patients (>18 years of age), c) intervention: supplementation with glutamine or omega-3 (enteral, parenteral, or both), d) study outcomes: mortality, length of ICU stay, total hospitalization, and incidence of infections.

Clinical studies that reported only biochemical, metabolic, nutritional, and immunological outcomes were excluded. Trials involving elective surgery patients admitted to the ICU, and research involving individuals receiving exclusive oral diets were also excluded. As a result of these search filters, fifteen publications were found, of which eleven met all the criteria established in this study, and the remaining studies were discarded. The selection phases were categorized and presented in a flowchart described in Figure 1, following the PRISMA group's recommendations.¹⁹

Figure 1 - PRISMA Flowchart for Study Selection.¹⁹



RESULTS

As a search filter resulted in the identification of eleven publications that met all the criteria established in this study, while the remaining studies were discarded. Table 1 provides a summary of the articles, including details on sample size, research design, interventions, and outcomes.

Chart 1. Matrix categorization of the studies included in the systematic review on the effects of immunonutrients on clinical outcomes in critical patients.

Author	Sample	Study design	Intervention	Outcomes	Results
Elamin, Miller & Ziad. ²⁰	17 Critically ill patients diagnosed with ARDS.	Double-blind, controlled, prospective, and randomized.	Patients in the experimental group received enteral immunomodulatory formula (EPA + GLA) for 7 days	Oxygenation, LIS, and MOD scores, duration ofMV, and length of stay in the ICU	Patients who received the immunomodulatory formula had a reduced length of stay in the ICU compared to the control group (12.8 days vs. 17.5 days)
Van Zanter et al. ²¹	301 adult patients requiring MV and enteral nutrition for more than 72 hours	Meta-plus, randomized, international, double-blind, multicenter	The IMHP group received enteral immunomodulatory formula enriched with glutamine, omega 3, and antioxidants for a maximum of 28 days	Mortality (in the ICU and at hospital discharge, at 28 days and 6 months), SOFA score progression, duration ofMV, incidence of new infections, length of hospital stays, and ICU stay	There was no statistically significant difference in new infections between the groups. Mortality in the IMHP medical subgroup was higher than in the group that received only a high-protein diet
Barros et al. ²²	Forty-nine patients between 60 and 80 years old admitted within the first 48 hours of ICU admission after hemodynamic stabilization	Prospective, controlled interventional	Patients in the intervention group were supplemented with a lipid emulsion rich in fish oil at 0.2g of lipids/kg of body weight for 6 hours on three consecutive days, approximately 2 and 4g of EPA and 1.2 and 2.4g of DHA	Mortality, length of stay in the ICU, and duration of MV	The mortality rate was higher in the control group (15 vs. 6). There was no difference in the length of ICU stay between the groups
Hosny et al. ²³	Seventy-five adult patients diagnosed with early sepsis	Double-blind, prospective, and randomized	Group A received high doses of DHA and EPA (9g) and antioxidants (selenium, ascorbic acid, and alpha tocopherol) orally or enterally for 7 days. In Group B, a low dose of omega-3 (3g) plus the same dosage of antioxidants was administered for the same period	Length of stay in the ICU, 28-day mortality, duration ofMV, infectious complications, inflammatory markers, SOFA score, among others.	No statistical significance was found in Group A and the control group regarding ICU length of stay and 28-day mortality

Chart 1. Matrix categorization of the studies included in the systematic review on the effects of immunonutrients on clinical outcomes in critical patients..(Continues)

Author	Sample	Study design	Intervention	Outcomes	Results
Hall et al. ²⁴	Sixtyadult patients with sepsis admitted to general and surgical ICUs and a general and surgical high dependency unit	Controlled, prospective, and randomized.	Participants in the experimental group received parenteral lipid emulsion containing fish oil (0.2g FO/kg/day) at a rate of 0.05g FO/kg/h daily until the 14th day or until discharge	Degree of organ dysfunction, length of stay in the ICU, total hospitalization, 28-day mortality, and hospital mortality	There was no reduction in 28-day mortality, ICU length of stay, and total hospitalization between the groups. Among sepsis classes, there was a significant decrease in mortality in patients with less severe sepsis
Parish et al. ²⁵	Fifty-eight patients admitted to two ICUs diagnosed with mild to moderate ARDS	Prospective, randomized	The intervention group received six omega3softgel capsules per day (2 capsules every 8 hours), providing 720 mg of ω -3, including 600 mg of EPA and DHA every 2 capsules	Length of stay in the ICU, hospital mortality, 28-day mortality rate, oxygenation, ventilation parameters and others	ICU length of stay did not show significance between the groups, nor did the adjusted mortality rate
Tihista & Echavarría ²⁶	Ninety-two patients admitted to the ICU with burns > 15% of the body surface area, with respiratory injury requiring MV for 6 days and receiving EN.	Double-blind, prospective, randomized	Both groups received enteral formula with low fat content; however, the lipid source in the experimental group consisted of 50% fish oil (8g of EPA and 20g of DHA per 100ml)	Mortality, duration of MV and hospitalization, infectious and non-infectious complications, duration of EN, and other outcomes	The occurrence of sepsis and septic shock combined was lower in the intervention group, as well as individually. Other infectious complications were reduced in these patients. There was no difference in mortality and total hospitalization between the groups
Martínez-Lozano, Ramos & Álvarez. ²⁷	Seventy-three critically ill patients in the postoperative period of major abdominal surgery requiring PN for at least 5 days	Phase III clinical trial, non-inferiority, single center, controlled, blind, and randomized	The intervention consisted of individualized PN composed of fish oil and MCT	Overall mortality (in the ICU, hospital, and at 6 months), length of stay in the ICU and hospital, nosocomial infections, duration ofMV, and inflammation markers	The infection rate in the experimental group was lower but not significant. The analysis of nosocomial infections in those who received PN for +/-7 days was higher and statistically significant. Length of stay in the ICU, total hospitalization, and mortality did not differ between the groups

Chart 1. Matrix categorization of the studies included in the systematic review on the effects of immunonutrients on clinical outcomes in critical patients..(Continues)

Author	Sample	Study design	Intervention	Outcomes	Results
Singer et al. ²⁸	One hundred ICU patients (APACHE II >15) on mechanical ventilation	Monocenter, prospective, randomized controlled, and double-blind	The intervention group received EN and PN enriched with omega3 for 28 days.	Variation in Pao2/Fio2 from one day, lung function, ICU complications, length of stay, mortality, days free of intensive care and others	The length of ICU and hospital stay was shorter in the omega-3 group, as well as 28-day mortality and mortality rate after the observation period (90 days), but none were statistically significant
Heyland et al. ²⁹	1218 adult patients on mechanical ventilation with one or more organ dysfunction related to acute illness	Double-blind, prospective, and randomized	Patients in the experimental group received glutamine supplementation intravenously (0.35g/kg/day) and enterally (30g/day)	Mortality at 14 and 28 days and in-hospital, six-month survival, duration of MV, length of stay in the ICU, total hospitalization, infectious complications, and multiple organ dysfunction	There was a trend toward increased 28-day mortality in patients who received glutamine supplementation, as well as higher in-hospital and six-month mortality in these patients. There was no significant effect of supplementation on infectious complications
Ziegler et al. ³⁰	150 postoperative patients from gastrointestinal, cardiac, or vascular surgery requiring PN in a surgical ICU	Double-blind, randomized, controlled, and multicenter	Isocaloric, isoproteic parenteral nutrition containing dipeptide alanil-GLN (0.5g/kg/day) for 28 days or until hospital discharge.	Incidence of new nosocomial infections, daily SOFA score, length of hospital stays, days free of MV and others.	There was no difference between the groups regarding the incidence of new infections, as well as all mortality indices analyzed. The total hospitalization time also did not differ among the study subjects

Source: The authors of the article. 2023. Captions: ARDS = Acute Respiratory Distress Syndrome; EPA = Eicosapentaenoic Acid; DHA = Docosahexaenoic Acid; LIS = Lung Injury Score; MOD = Multiple Organ Dysfunction; MV = Mechanical Ventilation; ICU = Intensive Care Unit; SOFA = Sequential Organ Failure Assessment; EN = Enteral Nutrition; PN = Parenteral Nutrition; MCT = Medium Chain Triglycerides; APACHE = Acute Physiology and Chronic Health Evaluation

DISCUSSION

This study aimed to investigate the outcomes of immunomodulation in critically ill patients, as specialized nutritional support in intensive care has been shown to improving the quality of life, particularly for septic patients or those at risk. According to the literature, immunonutrients have the capacity to promote benefits in lymphocyte function, combat infectious complications, and reduce mortality in critically ill patients.³¹

The study involved critically ill patients diagnosed with a condition that progressed to who received an immunomodulatory formula (GLA + EPA) for 7 days. A reduction in ICU length of stay was observed (12.8 vs. 17.5 days), although it was not statistically significant ($p=0.01$). Additionally, although not analyzed as an outcome, 28-day mortality was lower in the experimental group, but it did not reach statistical significance ($p=0.3$).²⁰

Similarly, Zanter et al.²¹ used a high protein enteral formula with immunomodulators (glutamine, omega-3, and antioxidants) for a maximum of 28 days to evaluate the incidence of new infections, mortality (up to ICU and hospital discharge, after 28 days, and at 6 months), SOFA score progression, duration of mechanical ventilation, ICU length of stay, total hospitalization, and other parameters in patients admitted to 14 intensive care units in different countries. The sample consisted of patients who required mechanical ventilation and parenteral nutrition for more than 72 hours and initiated this feeding route within 48 hours of admission to the intensive care unit. As results, there were no statistically significant differences between the groups regarding the occurrence of new infections and other clinical parameters, except for reduced mortality in the IMHP subgroup (95% CI, 40%-67%) compared to 35% mortality in the control group (95% CI, 22%-49%; $P=.04$).

Furthermore, the study conducted by Barros et al.²² parenteral supplementation containing EPA and DHA fatty acids, in a ratio of 20% and 12%, respectively, in hemodynamically stable patients admitted to the ICU for 6 hours on 3 consecutive days. Among the outcomes analyzed were SOFA and APACHE scores, mortality, ICU length of stay, duration of mechanical ventilation, among others. Mortality and duration of invasive ventilation were lower in the intervention group (40% vs. 44% and 9.54 ± 1.15 days in the control group vs. 6.85 ± 1.15 days in the FLE group; $p=0.15$), these differences did not reach statistical significance. Additionally, there was no significant difference in ICU days between the two groups (12.4 ± 1.6 days in the control group vs. 10.0 ± 1.6 days in the FLE group; $p=0.356$).

Similarly, Hosny et al.²³ obtained similar results in the analysis of the average ICU length of stay (11.6 ± 6.1 in group A vs. 13.9 ± 4.2 in the control group, $p=0.124$) and 28-day mortality (32% vs. 40%, $p=0.56$). In both studies, the data for the analyzed outcomes were better in the experimental group, but without statistical significance, which may be limited by the small sample size.

Furthermore, the study conducted by Hall et al.,²⁴ involving critically ill patients who received parenteral omega-3 fatty acid supplementation, did not identify a statistically significant relationship in the variable's mortality ($p=0.197$), ICU length of stay, and total hospitalization analyzed ($p=0.858$ and $p=0.796$, respectively). However, when analyzing the mortality rate among sepsis classifications, there was statistical significance in the reduction of mortality in the less severe sepsis subgroup ($p=0.041$).

Furthermore, the data demonstrated a significant reduction in the development of morbidity related to organ dysfunction. When analyzing the change in the SOFA score's impact on mortality, a reduction from 15.2% to 8.5% was found. Although this association was not intended to be related to mortality, it is a tool that can be used as a prognosis in critically ill patients.²⁴

Similarly, the research conducted by Parish et al.²⁵ also found no statistically significant differences between the groups in terms of mortality and ICU length of stay ($p=0.612$ and $p=0.524$, respectively). Among the limiting factors of this study is the non-blinding of the research, which may introduce bias, and the reduced sample size due to the chosen pathology as an inclusion criterion.

However, the results of the study conducted by Tihista and Echavarría²⁶ severely burned patients who received enteral nutrition with 50% of the lipid content containing EPA and DHA identified reduced infection rates, such as severe sepsis and septic shock ($p=0.03$), in the intervention group, as well as a lower trend in other infectious complications in this sample. MV duration was also shorter in this group, although not statistically relevant ($p=0.11$). The analysis of hospitalization time (average 65 ± 48.6 and 58 ± 43.5 , LF-EN group and FO-EN group, respectively) and mortality did not differ between the groups. Among the limitations of this research are, again, the small sample size, the absence of indirect calorimetry, and the brief time frame to analyze the outcomes of severely burned patients, who have a severe and prolonged course of illness.

The study conducted by Martínez-Lozano, Ramos & Álvarez,²⁷ which offered parenteral solution composed of soybean oil, MCT, olive oil, and fish oil in a proportion of 30%, 30%, 25%, and 15%, respectively, also found reduced infection rates in the sample that received the intervention, although it was not statistically significant ($p=0.559$). However, when analyzed within the subgroup that received PN for less than 7 days, the incidence of nosocomial infection was higher and statistically significant compared to those who received it for a longer period. Other clinical parameters did not differ between the groups, which may be justified by the small number of patients and the single-center nature of the research.

The research by Singer et al.²⁸ provided supplemental enteral and parenteral nutrition, both enriched with omega 3, for up to 28 days in individuals using MV allocated to the intervention group. As a result, there were more days free from intensive care (8.2 ± 9.1 vs. 6.7 ± 9.0 days in the omega-3 group and control group, $p=0.3567$), as well as reduced ICU length of stay and total hospitalization and mortality rates at 28 and 90 days in the omega-3 group, but without statistical significance ($p=0.6832$; $p=0.4544$; $p=0.8086$; and $p=0.5173$, respectively).

One of the limitations of this study is that it provided quantities of PUFAS based on calculated nutritional needs, rather than optimizing dosages. Additionally, the proportion of high-density lipids used by manufacturers may have limited the effects of omega-3. Similar studies that utilized a higher proportion of low-density fats achieved more favorable results.²⁸

Regarding studies conducted with glutamine, Heyland et al.²⁹ supplemented the amino acid (0.35g/Kg/ideal body weight) along with vitamins and antioxidant minerals intravenously in adult patients receiving mechanical ventilation and multiple organ failure related to acute illness for a maximum of 28 days, until ICU discharge or death. As a result, there was a trend of increased overall mortality at the end of the 28 days among patients who received glutamine compared to those who did not (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% CI, 1.00 to 1.64; $P=0.05$). In addition, in-hospital mortality and mortality at 6 months were significantly higher in the group that received the supplementation, but ICU length of stay and total hospitalization time did not show significant differences between the groups ($p=0.62$; $p=0.15$).

Another study by Ziegler et al.³⁰ also provided parenteral supplementation of dipeptide alanyl-GLN (0.5g/kg/day) along with NE with a non-enriched conventional formula with immunonutrients in patients admitted to a surgical ICU after cardiac, vascular, or gastrointestinal surgery who required PN for more than 7 days, also for a maximum period of 28 days of intervention. As a result, there was no difference in the total number of associated infections after initiation of intensive care ($p=0.70$), and it did not impact any of the

mortality indices evaluated between the groups ($p=0.88$). Data on days free from mechanical ventilation, ICU length of stay, and total hospitalization also showed no statistically significant differences.

According to some authors, the use of this amino acid has led to improvements in the incidence of hematological infections, reduced intestinal permeability, bacteremia, ICU length of stay, total hospitalization, and mortality in critically ill patients. Therefore, based on these findings, glutamine supplementation can help maintain plasma levels and improve the prognosis of patients in intensive care.^{6,7,31,32}

When comparing these clinical studies with the guidelines published on the subject, there is agreement in the absence of favorable data to support the routine use of immunonutrients in critically ill patients. The guidelines published by the American Society for Parenteral and Enteral Nutrition (ASPEN) in 2016 do not suggest the routine use of immunomodulatory enteral and parenteral nutrition. Immunomodulation should not be used routinely since most studies did not individually analyze the pharmaconutrients, nor their effects and appropriate dosages. The existing literature until 2016 was subject to several criticisms due to the heterogeneity of the studies, as they included a wide population of critically ill patients and various commercial formulas. Thus, the need for the use of specialized formulas should be carefully analyzed.³³

Regarding glutamine, there is a benefit in maintaining intestinal integrity but no potential to promote a systemic antioxidant effect capable of reducing mortality, infections, or hospitalization time. It is not recommended in critically ill patients except for trauma and major burns, according to the guidelines published in 2016 and 2019 by the American Society and European Society for Clinical Nutrition and Metabolism (ESPEN). Similarly, the use of anti-inflammatory lipid emulsions is not recommended by the 2016 guideline, considering the lack of studies that prove the attenuation of unfavorable clinical outcomes in this population. The updated guideline from 2022 suggests the use of mixed lipid emulsions or 100% soybean oil in eligible patients admitted to the ICU.³³⁻³⁵

When analyzing parenteral supplementation with fish oil-based lipid emulsions compared to soy-based ones, these guidelines suggest that such substitution may offer benefits. However, it is not possible to recommend this practice due to the limited variability of these products in the market until the publication of this guideline. Furthermore, studies using parenteral glutamine supplementation have yielded conflicting results regarding clinical outcomes such as mortality, which made the recommendation non-routine by ESPEN and ASPEN.^{32,33}

These recommendations align with the 2018 Brazilian guideline on nutritional therapy in critically ill patients established by the Brazilian Society for Parenteral and Enteral Nutrition (SBNPE), which does not endorse the routine use of immunomodulatory formulas in the ICU. The variability in study designs for this intervention (including dosage, components, and other characteristics), and the potential for harm remain poorly understood. The exception is the recommendation for the cautious use of immunomodulators in postoperative patients undergoing major surgeries when hemodynamically stable.³⁶

Furthermore, the use of EN with omega-3, borage oil, and antioxidants is not recommended in ARDS cases, according to expert opinions. Likewise, glutamine supplementation should not be routine, except in cases of burns and trauma, where it may be considered. This guideline recommends that lipid emulsions used in critically ill patients should be balanced with MCT, olive oil, and fish oil, and formulations based on soybean oil should be avoided. On the other hand, parenteral glutamine use is contraindicated in cases of multiple organ dysfunction, renal and hepatic dysfunction, or hemodynamic instability, according to the society's recommendation.³⁶

When comparing the studies found in this review with the evidence-based recommendation by responsible societies, there is a similarity in the absence of data supporting the use of immunonutrition in

critical illness. It was also possible to observe a reduction in clinical trials using such immunonutrients, especially glutamine, following the publication of the 2016 American guideline, which does not recommend routine use of these nutrients, making it difficult to analyze and compare the cost-benefit literature.

Among the limitations of this study, there is a scarcity of clinical research on the use of immunomodulators in critically ill patients in the last five years. The scarcity may be attributed to a decrease in the interventional research of this nature following the recent nutritional therapy guidelines in this population.

CONCLUSIONS

Recognizing the unique challenges associated with managing of critically ill patients. Particularly concerning nutritional considerations, evidence-based clinical practice is essential, especially in advising specific nutrients that regulate organic responses. Based on this, the analysis of the clinical studies that comprised this research and their effects on mortality, ICU length of stay, total hospitalization, and the incidence of infections demonstrated a lack of significant results to support the routine use of immunonutrients in critically ill patients. Therefore, further research is necessary to establish the true benefits of this approach.

It is suggested that future studies investigate the potential benefits of other immunomodulatory nutrients and incorporate functional outcome variables. The recommendation arises from the findings of this research, which did not demonstrate clear advantages in recommending the routine use of these substances for the outcomes analyzed. However, the potential benefits of these nutrients in relation to other parameters remain uncertain.

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Contributors

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