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SYSTEMATIC REVIEW
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Effect of Nutritional Support on Clinical Outcomes of Intensive Care Unit Patients

Pengaruh Nutritional Support *terhadap Luaran Klinis pada Pasien* Intensive Care Unit

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ABSTRACT

Background: Nutritional support is a globally acknowledged standard of care for critically ill patients, forming an integral component of clinical therapy in Intensive Care Units (ICUs) to enhance overall clinical outcomes.
Objectives: This study aimed to assess the impact of enteral nutritional support on clinical outcomes in ICU patients.
Methods: This research adopted a systematic review approach, focusing on Randomized Controlled Trial (RCT) studies conducted between 2010 and 2020. The review adhered to the PRISMA guidelines. The clinical outcomes studied included length of stay in the hospital, length of stay in the ICU, and mortality.
Discussion: Among 897 reviewed articles, only 6 articles were relevant. The study respondents were ICU in patients who received enteral formula, both in the control and intervention groups. The intervention group received an enteral formula featuring modified energy (normocaloric and high protein) and nutrients (enriched with pectin and immunse-modulating nutrients). Nutritional support in the form of enteral nutrition has varying effects on the length of hospitalization, ICU, and mortality.
Conclusions: No significant difference was observed in ICU and hospital stays between patients receiving standard enteral/hypocaloric/high protein nutrition and those receiving enteral nutrition enriched with pectin or immune-modulating nutrients. However, patients receiving enteral nutrition with immune-modulating nutrients experienced a reduced length of hospitalization. The administration of immune-modulating nutrients was associated with an increased risk of mortality at 60 and 28 days in critically ill patients.

INTRODUCTION

Patients facing critical conditions, such as those experiencing burns, severe trauma, surgery, and severe infections, require specialized treatment due to their high risk of malnutrition. Research indicates that approximately 40% of critical patients in the ICU suffer from malnutrition, and 60% of those cases are linked to digestive disorders, including motility and malabsorption issues[1]. Patients with digestive tract disorders may experience decreased nutritional intake, leading to reduced energy levels and muscle mass. Providing appropriate nutritional support to combat malnutrition and its associated complications is important. This support should be tailored to the patient's individual needs, focusing on providing the necessary macro and micronutrients[2]. Traditionally, nutritional support was primarily regarded as a form of supportive care. However, over time, it has emerged as a crucial treatment option for patients who experience metabolic stress, require protection against tissue damage from oxidative stress, and need to enhance their immune system. Additionally, nutritional support plays a vital role in safeguarding muscle mass, lowering infection risk, accelerating the healing process, maintaining digestive tract function, shortening hospitalization duration, and mitigating the risk of mortality[3]. Hence, a comprehensive literature review is imperative to determine the impact of nutritional support on clinical outcomes for critically ill patients in the ICU. This review is expected to serve as a valuable reference point for healthcare providers in delivering appropriate nutritional support to ICU patients. Specifically, this systematic review aimed to analyze all randomized controlled trials conducted between 2010 and 2020, with a focus on evaluating the impact of enteral nutrition on clinical outcomes in ICU patients.

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METHODS

Study Design

This study was designed as a systematic review, without incorporating a meta-analysis. The literature analyzed for this review comprises research articles employing Randomized Controlled Trial (RCT) designs, specifically on the impact of enteral nutrition as a form of nutritional support on clinical outcomes among ICU patients. The articles considered were published between 2010 and 2020. The methodology employed in this review adheres to the guidelines set forth by PRISMA[4].

Inclusion and Exclusion Criteria

Inclusion criteria were studies designed as RCTs with adult respondents aged over 18 admitted to the ICU. These studies must focus on specific clinical outcomes, such as the length of hospital stay, the length of stay in the ICU, mortality rates, and the use of enteral nutrition for patients. The exclusion criteria encompassed articles in press or accepted for publication, duplicated articles across databases, studies with general outcomes, pediatric emergency patients, and patients on ventilators.

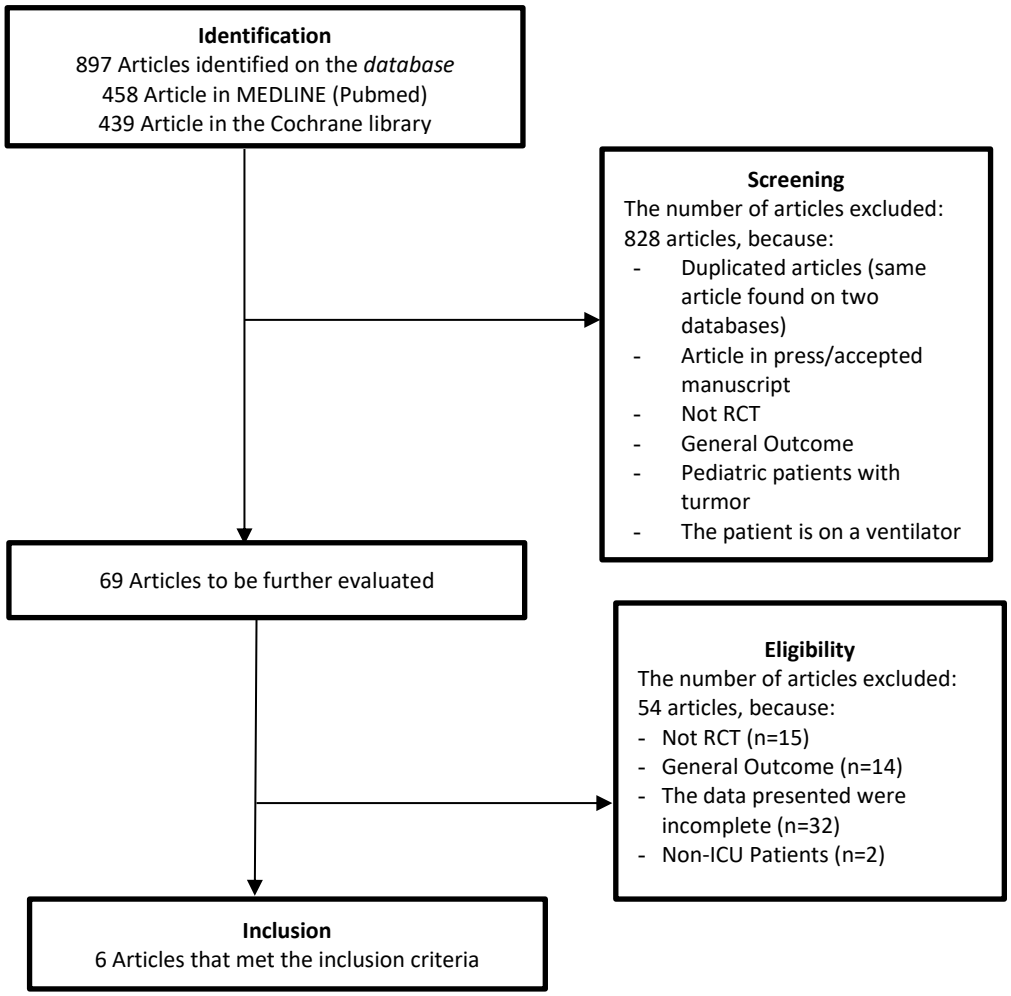

Image 1. Selection procedure of information sources (articles) reviewed in systematic research review

Intervention and Outcomes

After thoroughly reviewing randomized controlled trial research articles, we focused on interventions involving enteral nutrition. This type of nutrition was administered to patients in the form of either commercially available or hospital-made enteral nutrition. The outcomes assessed included mortality rates, length of hospital stay, and duration of enteral feeding while in the ICU.

Resources/Study Selection

Article searches were carried out on two electronic databases, MEDLINE (Pubmed) and the Cochrane Library, spanning the years 2010-2020. The articles were required to be in English and were searched using keywords such as “enteral nutrition on/en ICU patients” and “parenteral nutrition on/pn ICU patients.” Selected articles were those published and accessible, excluding those still in press or accepted manuscripts. Careful evaluation of interventions and outcomes was conducted to ensure relevance, with inclusion and exclusion criteria determined through title and abstract analyses.

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Data Collection/Extraction and Data Presentation

Each article underwent thorough screening for its title, abstract, research design, intervention provided, and respondents. Data gathered included hospitalization, ICU admission, and mortality rates. Data on the length of hospitalization and ICU stay were presented in mean and standard deviation (SD), while mortality data were presented as the number of mortality events in both hospital and ICU settings.

DISCUSSION

Article Filtering Results

A comprehensive search across two databases, MEDLINE and the Cochrane Library, resulted in the identification of 897 articles. These articles underwent thorough screening based on several parameters, such as abstract, year, research design, research variables, interventions, respondents, and research objectives. Following this screening process, six relevant articles were obtained, analyzing the effect of enteral nutrition on clinical outcomes - primarily mortality, length of stay in hospitals, and ICU stay - in ICU patients. The research design of all six articles was RCT, with control groups and interventions observed over a specific period to analyze clinical outcomes.

Respondents in this systematic review were ICU patients diagnosed with acute lung injury, gastrointestinal tract disorders, sepsis, postoperative, critical patients, head trauma, and stroke. All ICU patients received enteral feeding. These patients were divided into two groups: the control and the treatment/intervention group. The control group received enteral feeding with normocaloric and high-protein content. In contrast, the intervention group received enteral feeding with the addition of pectin, immune-modulating nutrients, omega-3, Eicosapentaenoic Acid (EPA)/Gamma-Linolenic Acid (GLA), and hypocaloric.

The review results of six selected articles showed that the 28-day mortality of ICU patients who received hypocaloric enteral feeding along with the addition of EPA/GLA (intervention group) was not significantly different from patients who received standard/normocaloric/enteral feeding without the addition of specific nutrients (control group)[5–7]. However, the 6-month mortality of ICU patients receiving enteral feeding with immune-modulating nutrients (intervention group) differed significantly from that of ICU patients receiving high-protein enteral feeding (control group). In this scenario, the intervention group exhibited a higher 6-month mortality compared to the control group. The immune-modulating nutrients utilized in the study were omega-3, glutamine, and antioxidants. The results of this systematic review are consistent with the results of six other studies, showing no significant difference in mortality rates among ICU patients who received normocaloric and hypocaloric enteral feeding[8]. Three other studies also showed similar results with these outcomes. A study conducted by Charles et al. (2014) involving 83 critically ill patients receiving eucaloric and hypocaloric enteral feeding with high protein intake targets showed no significant difference in mortality rates[9]. Similarly, Arabi et al. (2015) reported no significant difference in mortality rates among 894 ICU patients who received enteral feeding with standard calories and hypocalories[10]. Petros et al. (2014) also reported no difference in mortality rates among 100 ICU patients who received normocaloric and hypocaloric enteral feeding for at least 72 hours in the ICU[9].

The 28-day mortality in the hypocaloric enteral feeding group was not significantly different from the standard, as hypocaloric enteral feeding had little metabolic impact on patients. Enteral feeding with EPA/GLA was not significantly different from the group that received standard enteral feeding, this is attributed to the absence of organ failure in the study participants, who were in the early phase of sepsis[6]. However, enteral feeding with the addition of immune-modulating nutrients in the form of a combination of omega-3, glutamine, and antioxidants increased the mortality rate at 6 months. In the study, patients received enteral nutrition with a dose of EPA + DHA as much as 16.2 g per day during the 28 days of intervention. EPA + DHA intake from days 3-14 amounted to 0.07 g/kg body weight per day (average 5.6 g/day) and is still classified as a dangerous dose[11]. This is consistent with the Reducing Deaths Due to Oxidative Stress (REDOX) trial, where the administration of glutamine supplementation to patients can increase mortality without a concurrent rise in infection rates[12]. EDEN-OMEGA study showed that administration of omega-3, EPA, DHA, gamma linoleic acid, and antioxidants in patients with acute lung injury did not decrease 60-day mortality[13].

The results of the systematic review showed no difference in the length of stay in the ICU and hospital between ICU patients who received enteral feeding normocaloric and hypocaloric. This similarity is because protein intake from the two groups is low, which increases the risk of infection. This study aligns with the research by Charles et al. (2014), which revealed no difference in the length of stay in the ICU and hospital in 83 critical patients who received eucaloric and hypocaloric enteral feeding[9]. Similarly, Arabi et al. (2015) reported no significant difference in the length of stay in the ICU among 894 patients who received enteral feeding with standard calories and hypocaloric[10]. Results of systematic review and meta-analysis of six other studies also supported these findings, indicating no significant difference in the length of stay in the ICU in patients who received normocaloric and hypocaloric enteral feeding[8].

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Table 1. Summary of articles that fit the inclusion criteria

No	Researchers and Years	Title and Subject of Research	Method	Results and Conclusions
1.	Fengchan et al., 2017	**Title** Efficacy and safety of pectin-supplemented enteral nutrition in intensive care: a randomized controlled trial **Subject** Patients in the ICU who received enteral tube feeding	**Research Design** RCT **Intervention** A total of 166 ICU patients were divided into two treatment groups. The control group received the standard enteral formula, while the intervention group was administered the same enteral formula with pectin as an additive, for 7 days.	**Results** The study results indicated that the mortality rate was 4.8% in the control group and 1.61% in the intervention group (p = 0.317). The length of ICU stay (17.9±9.72 vs 13.8±8.59, p<0.001) and hospital stay (32.9±19.0 vs 23.4±13.2, p<0.001) between the control and intervention groups. **Conclusion** Enteral formulas that contain pectin are safe for ICU patients and may enhance clinical outcomes.
2.	Ibrahim ES et al., 2018	**Title** Enteral nutrition with omega-3 fatty acids in critically ill septic patients: a randomized double-blinded study **Subject** Critically ill patients with sepsis received enteral feeding	**Research Design** Randomized double-blinded study **Intervention** A total of 110 septic patients were divided into two groups. Group A was administered an enteral formula containing 1000 mg of Omega-3 per serving, thrice daily, while Group B received the same enteral formula without Omega-3.	**Results** Duration of stay in ICU was longer in Group B (p=0.019). However, post-ICU hospital stays were similar in both groups. Notably, there was no significant difference in mortality rates between the two groups. **Conclusion** Omega-3 has no significant impact on reducing mortality rates or shortening the length of hospital stay after patients are discharged from the intensive care unit.
3.	Mousavian et al., 2020	**Title** Randomized Controlled Trial of Comparative Hypocaloric vs. Full-Energy Enteral Feeding During the First Week of Hospitalization in Neurosurgical Patients at the Intensive Care Unit **Subject** Patients in the ICU who had undergone trauma, suffered a stroke, or undergone neurosurgery	**Research Design** RCT **Intervention** A total of 58 patients were divided into two groups for a clinical study. The full-energy enteral feeding group received an enteral formula with an energy content of 75% of the requirement, which was gradually increased to 90-100% of the energy requirement over seven days. The hypocaloric enteral feeding group was administered an enteral formula with an energy content of 30% of the requirement, which was gradually increased to 75% of the requirement for seven days.	**Results** The length of stay in the hospital was lower in the hypocaloric group compared to the full-energy group (P = 0.046). However, no significant difference was shown in ICU length of admission (p = 0.163), and mortality of 28 days (P = 0.640). **Conclusion** Hypocaloric enteral feeding is related to a long decrease in inpatient care in hospitals.
4.	Pontes-Arruda et al., 2011	**Title** Enteral nutrition with eicosapentaenoic acid, g-linolenic acid, and antioxidants in the early treatment of sepsis: Results from a multicenter, prospective,	**Research Design** Multicenter, prospective, randomized, double-blinded, controlled study **Intervention**	**Results** The group receiving enteral formula with EPA/GLA had a shorter length of stay in the ICU and hospital compared to the group receiving enteral formula

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No	Researchers and Years	Title and Subject of Research	Method	Results and Conclusions
		randomized, double-blinded, controlled study: The INTERSEPT Study **Subject** Patients in the ICU who were diagnosed with sepsis early on may benefit from enteral feeding	A total of 115 patients were divided into two groups: one group received the enteral formula with EPA/GLA, and the other received the enteral formula without EPA/GLA.	without EPA/GLA. However, there was no significant difference in mortality rates between the two groups. **Conclusion** The enteral formula containing EPA/GLA affects the length of stay in early sepsis without organ dysfunction.
5.	Rugeles et al., 2013	**Title** High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients: a randomized clinical trial **Subject** Patients in the adult ICU receiving enteral formula	**Research Design** RCT **Intervention** A total of 240 patients were divided into two groups. One group received an enteral hypocaloric formula (15 kcal per kg body weight per day), while the other group received an enteral normocaloric formula (25 kcal per kg body weight per day).	**Results** There were no significant differences in the length of stay in the ICU or mortality between the two groups. **Conclusion** There is no difference in clinical outcomes between enteral formulas with hypocaloric and normocaloric nutrition.
6.	Zanten et al., 2014	**Title** High-Protein Enteral Nutrition Enriched with Immune-Modulating Nutrients vs Standard High-Protein Enteral Nutrition and Nosocomial Infections in the ICU: A Randomized Clinical Trial **Subject** Patients in the ICU receiving enteral feeding	**Research Design** RCT **Intervention** A total of 301 ICU patients were divided into two groups. One group received an enteral formula containing immune-modulating nutrients, including omega-3 (EPA and DHA), glutamine, and antioxidants, while the other group received a high-protein enteral formula administered for a maximum of 28 days.	**Results** There was no significant difference in length of stay in hospital and ICU between groups. However, there was a significant difference in the 6-month mortality rate (54% of the group that received enteral formula with immunonutrients and 35% of the group that received high-protein enteral formula). **Conclusion** Enteral formulas with immune-modulating nutrients could harm ICU patients by increasing mortality.

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This study showed no difference in the length of stay in the ICU and hospital for patients who received enteral feeding containing immune-modulating nutrients with high protein. However, contrasting results were observed in other studies where patients receiving enteral feeding containing EPA/GLA had a shorter duration of stay in the ICU and hospital compared to the control group who received standard enteral feeding. Similar findings were noted in the group receiving enteral feeding with pectin compared to the control group. In contrast, patients receiving enteral feeding containing omega-3 showed a shorter ICU hospitalization duration than those who did not receive omega-3, although the overall duration did not differ significantly. Omega-3, as an immune-modulating nutrient, can reduce proinflammatory cytokines, infection risk, and shorten the length of hospitalization[14]. Although omega-3 has anti-inflammatory effects, consumption of omega-3 in the form of EPA and DHA at a dose of 5.6 grams per day has the potential to harm critical patients and increase the risk of mortality within 28 days[11]. As was found in other studies, immune-modulating nutrients in enteral feeding have varying impacts on the length of stay in the ICU and hospitals. Three RCTs showed a decrease in length of stay in the ICU in patients receiving enteral formulas with omega-3s and antioxidants compared to high-fat formulas[12]. Other 17 RCT articles showed that administration of omega-3 through both enteral feeding and parenteral in critical patients can reduce the length of stay in the ICU and hospital[15–17].

CONCLUSIONS

Based on the study results, it can be concluded that the length of stay in the ICU and hospital was not significantly different between patients who received standard enteral nutrition/hypocaloric/high protein from patients who received enteral nutrition enriched with pectin or immune-modulating nutrients. However, patients receiving enteral nutrition with immune-modulating nutrients had a reduced length of hospitalization. Importantly, the administration of immune-modulating nutrients may elevate the risk of mortality at both 60 and 28 days in critical patients.

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Author Contributions

LBH: conceptualization, methodology, writing–review, and editing; CYD: methodology, review, and editing; AZF: methodology and editing.

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