SYSTEMATIC REVIEW/META-ANALYSIS

# Clinical Outcomes of Hypocaloric/Hyperproteic vs Normocaloric Enteral Feeding in the Acute Phase of Critical Illness among Patients Admitted in the Intensive Care Unit: A Systematic Review with Meta-analysis

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## Abstract

**Objectives:** To examine the effect of hypocaloric/hyperproteic enteral feeding vs normocaloric feeding on the survival of critically ill patients in the acute phase in the intensive care unit (ICU).

**Methodology:** Randomized clinical trials utilizing hypocaloric, hyperproteic, and normocaloric enteral feeding in the ICU were searched using the following terms ((((critically ill) OR (intensive care) OR (mechanically ventilated)) AND ((low-calorie enteral feeding) OR (high-protein enteral feeding)))) in MEDLINE, PubMed, Scopus, and Google Scholar by two independent authors.

**Results:** There were no significant differences in hospital mortality [odds ratio (OR), 1.0; 95% confidence interval (CI), 0.77, 1.31; $p = 0.99$, $I^2 = 0\%$], days on mechanical ventilation (MD, −0.05; 95% CI, −0.37, 0.28; $p = 0.78$, $I^2 = 0\%$), the odds of acquiring infectious complications (OR, 0.90; 95% CI, 0.71, 1.14; $p = 0.38$, $I^2 = 0\%$), and the length of ICU stay (MD, 0.60; 95% CI, −2.39, 3.59; $p = 0.69$, $I^2 = 96\%$). The length of hospital stay was significantly lower by 4.18 days in the normocaloric group (MD, 4.18; 95% CI, 2.50, 5.85; $p < 0.00001$, $I^2 = 0\%$).

**Conclusion:** This meta-analysis showed no significant differences in mortality, infectious complications, days of mechanical ventilation, and ICU length of stay between groups. Findings on hospital length of stay were interpreted with caution due to the low quality of evidence and clinical heterogeneity.

**Keywords:** Critically ill, Enteral feeding, High protein, Hyperproteic, Intensive care, Low calorie, Mechanically ventilated, Normocaloric.

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## Highlights

This systematic review shows that hypocaloric/hyperproteic enteral feeding does not consistently improve mortality, infection rates, or mechanical ventilation duration in critically ill patients. Quality of evidence and clinical heterogeneity complicate results. While higher protein intake may help, more research is needed. Current guidelines stress adequate nutrition despite mixed outcomes.

## Introduction

Disease-related malnutrition has always been a concern for critically ill patients because of continuous inflammation caused by increased catabolism. This leads to increased complication and mortality.[1] Specialized nutritional regimens have been proposed and successfully developed to reduce the negative effects of disease-associated malnutrition.[2] The European Society of Enteral and Parenteral Nutrition has suggested hypocaloric feeding (<70% of the total caloric requirement) in the early acute phase (days 1–2) and titrated to 80–100% of the total energy requirement in the late acute phase.[3] However, there is debate surrounding caloric intake in critically ill patients. Some cluster randomized controlled trials that compared full-caloric feeding with standard feeding did not show an improvement in mortality. It has also been suggested that hypocaloric feeding or underfeeding during the acute phase does not increase mortality and may even offer benefits in terms of gastrointestinal tolerance.[4] In contrast, a meta-analysis on the effect of low-and high-caloric intake found no association between the two doses and mortality but revealed a lower risk of bloodstream infection and renal replacement therapy among critically ill adults who were given hypocaloric enteral feeding.[5] Factors such as population heterogeneity, delivery methods or feeding routes, timing of feeding, and use of parenteral nutrition are the subjects of discussion in many of these trials.[5] In addition, the issue of whether to focus on calorie or protein provision and its impact on outcomes has been a constant issue for many years.[2,6,7] Most trials have not addressed protein issues or provided basic guidelines for protein delivery. Previous trials have shown that adequate protein delivery may be a crucial factor for nutrition delivery to improve outcomes in the intensive care unit (ICU).[2,8] The clinical benefits that

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have long been attributed to a high caloric content may be due to high protein levels.[9] Guidelines, particularly from ESPEN, mostly recommend high-protein provision (>1.2 gm/kg/day), but with no robust evidence to support it. In most studies, it is not possible to examine the effect of energy from proteins as both are interlinked. Mortality was observed when two variables (energy and protein) were combined. When two separate analyses were performed, little difference in the statistical variation was observed.[2]

In the past decades, many observational studies have explored the connection between caloric intake and outcomes, such as duration of ventilation support, length of hospital and ICU stay, bloodstream infections, overfeeding, and refeeding syndrome. Earlier observational studies suggest that maximizing nutrition with high-calorie intake or increasing calorie intake from 25 to 66% or closer to the goal may be associated with clinical benefits.[6] In a large database trial, it appeared that the optimal calorie dose in enteral nutrition (EN) for at risk critically ill patients is between 30 and 70% of the predicted calorie intake, as it resulted in the lowest 30-day mortality. In this same study, different hypothetical protein diets were compared and showed that late (day 5–11) high-protein feeding (>1.2 gm/kg/day) compared with exclusive low-protein diet (<0.8 gm/kg/day) was associated with lower in-hospital death.[3,10] A prospective observational study also evaluated the feasibility of increasing protein intake by measuring 24-hour urinary nitrogen excretion and showed improved nitrogen balance and energy intake without increasing the incidence of overfeeding.[11] However, randomized controlled trials, past and current time, have raised doubts about the findings. This may be due to the selection bias commonly found in many studies and other factors likely influencing the results, such as frequent feeding interruptions in the ICU, attrition, and performance bias. Unfortunately, evidence from these randomized trials also provided mixed and conflicting results regarding the benefits of full enteral feeding, the need for supplementation with parenteral solution, and the need for amino acid supplementation to prevent loss of lean body mass.[12,13]

Since there is no clear consensus on the optimal nutrient regimen for critically ill patients, we performed a systematic review and meta-analysis to explore the association between the dose and type of EN (hypocaloric/hyperproteic vs normocaloric) and clinical outcomes in this special population.

## Methodology

### Study Design

This systematic review and meta-analysis included studies on the impact on patient outcomes of early hypocaloric and hyperproteic vs normocaloric enteral feeding in the acute phase of illness (days 1–7) in critically ill adult patients (Appendix A and B). The protocol was performed in accordance with the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol (PRISMA) 2020 statement (Appendix C). This study was registered under the Registered Grants Administrative Office (RGAO), University of the Philippines Manila, identification number RGAO-2022-0554 (Appendix D), and Prospectively Registered Systematic Reviews (PROSPERO) CRD42021283247 (Appendix E).

### Search Strategy

We performed a thorough literature search of three electronic databases for articles published through October 2023. The databases used included MEDLINE, PubMed, Scopus, and Google Scholar. The search string implemented was: ((((critically ill) OR (intensive care) OR (mechanically ventilated)) AND ((low-calorie enteral feeding) OR (high-protein enteral feeding)))). The search criteria were further filtered to include only articles published in the last 15 years and on the adult human population. The investigators manually searched the bibliographies of all selected articles, gray literature, systematic reviews on nutritional support in critically ill patients, and studies presented as abstracts at the meetings of the American Society for Parenteral and Enteral Nutrition, the European Society for Parenteral and Enteral Nutrition, and the Philippine Society for Parenteral and Enteral Nutrition. In addition to the database search, any potentially relevant major journals and studies were cross-referenced with records from the electronic database search to discover any further research for inclusion. The reference lists of the articles that satisfied the inclusion and exclusion criteria were further examined to identify other relevant studies.

### Selection Criteria

Studies were included if they were: (1) Randomized Controlled Trials, (2) adult patients who were critically ill and/or mechanically ventilated for at least 7 days, (3) required EN for at least 48 hours, (4) primarily compared two doses of EN and reported caloric intake either in absolute values (i.e., in kcal or Cal) or in percentage of caloric or protein requirement as defined by the authors of the studies included, and with no specific disease criterion.

Any disagreements were resolved through multiple discussions between the main author, the co-author, and the statistician.

### Selection Process

The primary investigator and co-author independently assessed the titles for possible inclusion. Abstracts of eligible titles were screened, and articles were retrieved and screened for inclusion.

The trials included in this systematic review should have the following characteristics: One intervention should contain caloric restriction, which was defined as an intentional reduction in calorie intake below the computed requirement, and the hypocaloric dose should include trophic feeding (minimal amounts of calories, i.e., 10–15 kcal/day or maximum of 500 kcal/day) and permissive underfeeding (<70% of the total energy requirement per day). In this study, hyperproteic or high-protein enteral feeding was defined as equal to or >1.2 gm/kg/day or a protein content of >20% of the total required calories.

### Data Collection and Extraction

Using a standardized form, two non-blinded reviewers separately extracted pertinent data from the trials. The study design, size, setting, patient population, reported illness severity score, interventions and their duration, and calorie intake (mean and percentage of estimated caloric target) in each arm were among the information extracted. The primary outcome of this study was in-hospital mortality. If hospital mortality was not reported, 28-, 30-, 60-, 90-, or 180-day mortality rates were used. Secondary outcomes included hospital and ICU length of stay, infectious complications (which can be any infection or development of sepsis if specific types of infections are not reported), and mean days of mechanical ventilation.

### Study Risk of Bias Assessment

The Cochrane Collaboration tool was used to assess the risk of bias and the quality of the included studies. This assessment tool considers the internal validity of studies by examining sequence

generation; blinding of participants, personnel, and outcome assessors; and whether there was selective outcome reporting. The lead investigator and co-investigator independently assessed the methodological quality of each study using the Cochrane Collaboration technique to assess the risk of bias. Disagreements between the two reviewers were resolved.

### Statistical Analysis (Meta-analysis)

Continuous variables were presented as means or medians with their corresponding standard deviations or ranges, while categorical variables were presented as proportions. Categorical outcomes, including mortality and the proportion of patients who developed complications, were compared and summarized between the exposure and control groups using odds or risk ratios, while the mean difference represented by Hedge's G between the two groups was used for continuous outcomes, such as length of hospital and ICU stay, and days on mechanical ventilation. A forest plot for each outcome that contained the included studies, including their respective treatment effects, corresponding 95% confidence intervals, and weight, was also plotted. The forest plot contained the summary treatment effect, a *z*-test to determine the significant difference between the two interventions, and the Q and I2 tests to determine heterogeneity. A high Q value and >50% I2 indicated heterogeneity. Sensitivity tests were also conducted to rule out possible confounders and effect modifiers, and to decrease heterogeneity. As treatment outcomes were assumed to be heterogeneous, a random effects model was used in the analysis. All data were inputted and analyzed in RevMan 5.4.1, with a *p*-value of $< 0.05$, as a marker for significance.

## Results

### Description of the Studies

The final database search was completed in October 2023. A total of 646 records were searched and reviewed. Of these, 104 were duplicates, one was a retracted article, and 511 were excluded after title and abstract screening. During the final search, 32 studies were assessed for eligibility, and six (6) were included in the final analysis, meeting the inclusion criteria. The analysis comprised 1,435 enrolled participants who met the eligibility criteria. The PRISMA flow diagram describes the process of research selection along with the reasons for the exclusion of studies (Appendix C).

All included studies were randomized controlled trials written in English and conducted in tertiary teaching hospitals. All trials involved critically ill patients admitted to a medical ICU, a surgical ICU, mixed, or a neurosurgical unit, with various indications for admission to the ICU (Table 1). All studies compared hypocaloric and hyperproteic feeding with normocaloric feeding with varying amounts of protein.

### Descriptive Results

#### *Included Studies*

Six (6) studies fulfilled the following inclusion criteria: Arabi et al. (2015), Rugeles et al. (2013, 2016), Charles et al. (2014), Mousovian et al. (2020), and Rice et al. (2011).

#### *Study Settings*

The included studies were two (2) from the USA, one (1) from Saudi Arabia and Canada, one (1) from Iran, and two (2) from Colombia. Most studies were conducted in tertiary hospitals.

#### *Study Participants*

The ICU indications for admission reported in the studies were medical, surgical, mixed medical-surgical, and neurosurgical cases. One study (Rice et al., 2011) examined patients with acute respiratory failure. In another study (Rugeles et al., 2013) mostly studied medical cases (respiratory, CNS, cardiac, and gastrointestinal). By contrast, Charles et al., mostly involving surgical cases with various indications. The rest of the included studies examined mixed medical-surgical patients, ranging from admissions from the emergency department to surgical patients from both trauma and non-trauma causes, vascular and liver transplant patients, and neurological cases from stroke and trauma. The mean age of the participants was 50.4 with a comparable number of males and females. Upon admission to the ICU, the participants had an average BMI of 26.9. The patients were variably sick, with a mean Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) score of 17.9, ranging from 13.5 to 32.9 being the sickest (Table 1).

A total of 716 patients were randomized to the hypocaloric or hyperproteic group, while 719 participants were randomized to the control or normocaloric group. Participants in the studies were admitted to the ICU for at least 7 days and/or were dependent on mechanical ventilation for at least 48 h, requiring EN.

### Study Design and Intervention

All investigations used a parallel group design, with all trials comparing hypocaloric and normocaloric enteral feeding. Four of the included trials (Rugeles et al. 2013, Rice et al. 2011, Charles et al. 2014, Rugeles et al. 2016) which expressed intervention dose in kcal/day had an average of 13.5 kcal/day (<70% of the total caloric requirement) in the hypocaloric group as compared with the 24.55 kcal/day of the normocaloric group. Two other studies (Arabi et al. 2015 and Mousavian et al. 2020) that expressed calories as percentages reported a mean hypocaloric dose of 45% of the total computed requirement. Mean protein intake on the other hand from both hypocaloric and normocaloric groups are 1.5 gm/kg/day and 1.46 gm/kg/day respectively (Table 2).

### Risk of Bias in the included Studies

All six (6) studies included had a high risk of bias in at least one domain. One study had a high risk of selection bias (Charles et al. 2014). There was no specific mention of whether the allocation was properly concealed, or whether the participants were blinded to the intervention (unclear risk). Two studies (Charles et al. 2014 and Rugeles et al. 2013) were both at a high risk of attrition bias. Although most of the outcomes were objective or well-defined, with little danger of detection bias, healthcare personnel's descriptions of the treatment processes were insufficient to judge whether this could have resulted in a performance bias (Table 3).

### Effects of Intervention

#### *Mortality*

In Rice et al. (2011), both groups had the same number of days alive during the 28-day study period. One important finding was that survivors in the full-energy group were more likely to be discharged home rather than to a rehabilitation facility than those in the trophic group were. Subgroup analyses, including patients with acute lung injury, sepsis, or pneumonia as their admitting diagnosis, and patients with a BMI of 35 or higher, produced similar outcomes between the trophic and full-energy groups. In Arabi et al. (2015), there were no significant differences in either the primary

**Table 1:** Characteristics of the Studies Included in the systematic review

| *Title* | *Authors* | *Population* | *Year* | *Intervention* | *Outcome measured* | *Study design* | *Duration of Intervention* | *Count* | *Age* | *Male%* | *APACHE II* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit; a randomized controlled trial | Charles, Petroze, Metzger et al., 2014 | Surgical/ Trauma | 2014 | Hypocaloric nutritional support | • Number of infections per patient<br>• Percentage of patients acquiring infection<br>• Low length of stay<br>• Hospital length of stay<br>• 0600 Glucose concentration<br>• Number of mortalities | RCT | At least 72 hours | 83 | 51.9 | 68.3 | 16.9 |
| High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients; A randomized clinical trial | Rugeles, Angulo, Gutierrez et al., 2016 | Respiratory/ Neurologic | 2016 | Hyperproteic, hypocaloric enteral nutrition, normocaloric enteral nutrition | • Change in sequential organ failure assessment (Sofa) Score (ΔSOFA) from baseline at 48 hours<br>• Change in sofa score (ΔSOFA) from baseline at 96 hours<br>• Insulin Requirements<br>• Hyperglycemia or hypoglycemic episodes<br>• Length of ICU stay<br>• Days on Ventilator | Rand-omized parallel arm clinical study | 7–28 days | 120 | 52.8 | 50 | 13.6 |
| 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 | Mousavian, Pasdar, Ranjbar et al., 2020 | Trauma/ Stroke/ Neurosurgery | 2020 | Hypocaloric vs full energy enteral feeding | • Incidence of severe gastrointestinal intolerance<br>• Duration of mechanical ventilation<br>• Length of hospital stay<br>• Length of ICU admission<br>• 28-day mortality | RCT | 7–14 days | 58 | 41 | 68 | 19.1 |
| Permissive underfeeding vs standard enteral feeding in critically ill adults | Arabi, Aldawood, Haddad et al., 2015 | Mixed medical | 2015 | Hyperproteic hypocaloric enteral feeding | 90-day all-cause mortality,<br>• 28-day mortality, in-hospital mortality, 180-day mortality<br>• Serial SOFA scores | RCT | Up to 14 days | 894 | 50.5 | 67.6 | 21 |

*(Contd...)*

**Table 1:** *(Contd...)*

| *Title* | *Authors* | *Population* | *Year* | *Intervention* | *Outcome measured* | *Study design* | *Duration of Intervention* | *Count* | *Age* | *Male%* | *APACHE II* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hyperproteic hypocaloric enteral nutrition in the critically ill patient: A randomized controlled clinical trial | Rugeles, Rueda, Diaz et al., 2013 | Respiratory/ Neurologic | 2013 | Hyperproteic hypocaloric enteral feeding | Delta SOFA 48 hours<br>• Delta SOFA 96 hours, total SOFA scores<br>• ICU Length of Stay<br>• Days on ventilator<br>• Hyperglycemia or hypoglycemia<br>• Number of mortalities | RCT | 7–21 days | 80 | 54.5 | Equal | 14.5 |
| A Randomized trial of initial trophic vs Full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure | Rice, Morgan, Haye et al., 2011 | Medical/ Mechanically-ventilated | 2011 | Initial low volume (i.e. trophic) enteral nutrition, initial full energy enteral nutrition | • Ventilator free days to day 28<br>• Duration of enteral nutrition<br>• Mortality to hospital Discharge<br>• Episodes of diarrhea<br>• Episodes of elevated gastric residual volumes | RCT | 6–28 days | 200 | 53.5 | Female predominant | 26.9 |

endpoint of 90-day mortality, ICU mortality, in-hospital mortality, 28-day mortality, or 180-day mortality. Survival estimates, as seen in the Kaplan–Meier analysis, showed no significant difference in the probability of survival between the two groups. Subgroup analyses of the prespecified subgroups showed no significant differences in the primary outcome of 90-day mortality, with no significant interaction effects for any of the subgroups. Charles et al. (2014)**,** in mortality as a secondary outcome and Rugeles et al. (2016) also revealed no significant differences in 28-day mortality. Lastly, the 28-day mortality was higher in the hypocaloric group but not statistically significant in the Mousavian et al. (2020) study.

## Secondary Outcomes

### *Days in Mechanical Ventilation (MVD)*

Both the Mousavian et al. (2020) and Rice et al. (2011) trials showed that the intervention group was more beneficial, but not significant, in both Rugeles et al. (2013) and Rugeles et al. (2016). Arabi et al. (2015), on the other hand, used mechanical ventilation-free days as the variable for comparison and showed no difference between the two groups.

### *Length of Hospital Stay*

There was no significant difference between the groups in Rice et al. (2011), expressed as the number of hospital-free days. Secondary outcomes, including length of hospital stay in Charles et al. (2014) and Arabi et al. (2015), were also not different between the two groups. In contrast, Mousavian et al. (2020) revealed that the length of hospital stay in the hypocaloric group was significantly less.

### *Length of ICU Stay*

There were no significant differences in the number of ICU-free days and ICU length of stay (secondary outcome) in Rice et al. (2011) and Rugeles et al. (2013). There was also no significant difference in Arabi et al. (2015) and Rugeles et al. (2016). The length of ICU stay was comparable between the two groups in Mousavian et al. (2020).

### *Infectious Complications*

The incidence of infections and nosocomial pneumonia was similar between the two groups in Rice et al. (2011). The number of infections or the percentage of patients with infections between the two groups was not significant, as was the type of causative organism of the infections in the study by Charles et al. (2014). The subgroup analyses by sex and trauma did not differ. This trial found no evidence to support the hypothesis that hypocaloric feeding reduces the risk of infection compared with normocaloric feeding in patients admitted to a surgical/trauma unit. Patients who received <80% of their goal kilocalories were at the same risk of developing an infection as those who received 80% or more of their goal kilocalories. This finding is supported by a trial by Arabi et al. (2015), which also showed no statistical difference in ICU infections. Specifically, in Mousavian et al. (2020), the incidence of pneumonia did not show a significant difference between the groups, but the rate of multiorgan dysfunction syndrome was significantly lower in the hypocaloric group.

## Meta-analysis

### *Mortality*

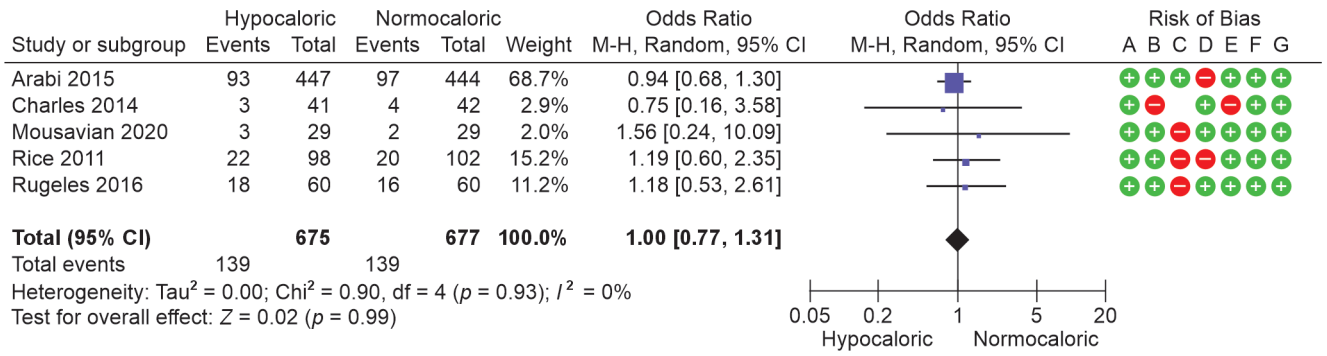
We analyzed five (5) trials (Arabi et al. 2015, Charles et al. 2014, Mousavian et al. 2020, Rice et al. 2011, Rugeles et al. 2016) that evaluated the outcome of interest with a total of 675 participants. We found low-statistical heterogeneity ($I^2$ = 0%) with a range of

**Table 2:** Summary of the enteral feeding interventions (in kcal/kg/day for calories, gm/kg/day for protein, or percent)

| | *Hypocaloric group energy* | *Hypocaloric group protein* | *Normocaloric group energy* | *Normocaloric group protein* |
|---|---|---|---|---|
| Charles, Petroze, Metzger et al., 2014 | 12.3 | 1.5 | 17.1 | 1.5 |
| Rugeles, Angulo, Gutierrez et al., 2016 | 12.6 | 1.39 | 25 | 1.42 |
| Rugeles, Rusda, Diaz et al., 2013 | 15 | 1.5 | 25 | 0.76 |
| Mousavian, Pasdar, Ranjbar et al., 2020 | 12.8 | 34g/d or 44% | 20 | 54g/d or 70.1% |
| Rice, Morgan, Haye et al., 2011 | 300 kcal/day, 15.8% | 54.4g | 1418 kcal/day 74.8% | 10.9g |
| Arabi, Aldawood, Haddad et al., 2015 | 46% | 57g | 71% | 59g |

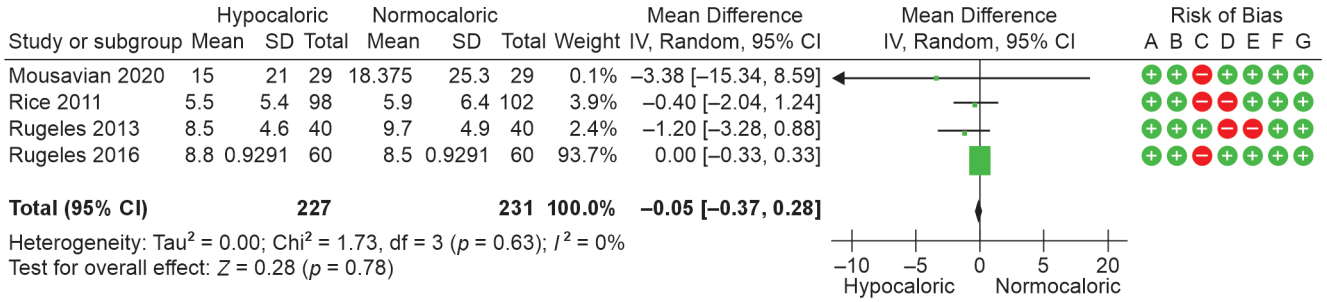
**Table 3:** Risk of Bias in the Included Studies

| *Study* | *Allocation bias* | *Blinding (performance and detection bias* | *Incomplete outcome (attrition bias)* | *Selective reporting* | *Other potential biases* |
|---|---|---|---|---|---|
| Charles, Petroze, Metzger et al., 2014 | Allocation concealment not detailed | Single-blind (investigator) | Study was closed before full enrollment of 116 patients; reason is slow enrollment | None | There was a misconception held by family members signing consent that patients would be intentionally starved if randomly allocated to the hypocaloric arm, making consent difficult to obtain |
| Rugeles, Angulo, Gutierrez et al., 2016 | Randomized | Single-blind (patients) | Reporting properly observed and complete | None | Doubts on proper blinding of ICU staff; power calculation specifically calculated for ΔSOFA; use of soy protein may be debatable due to possible low biologic value and poor tolerance |
| Mousavian, Pasdar, Ranjbar et al., 2020 | Randomized | Single-blind (patients) | Reporting observed and complete | None | Small sample size, the use of HBEs to estimate the energy requirements in the patients with MV which may not be highly accurate, and the use of the bolus feeding method instead of a continuous nutrition support method which may have improved the gastrointestinal tolerance of the patients in the full energy group |
| Arabi, Aldawood, Haddad et al., 2015 | Randomized | Unblinded | Reporting properly observed and complete | None | Only 14% of the patients who were admitted to the ICU and screened were included; the target caloric intake was not reached in some patients, particularly in the standard feeding group; did not have a formal adjudication process for the secondary outcome of infections |
| Rugeles, Rueda, Diaz et al., 2013 | Randomized | Single-blind (ICU staff) | Only 80 out of 115 potential patients were included; reason for exclusion is early ICU discharge | Mortality data lacking; not pre-specified | Low statistical power |
| Rice, Morgan, Haye et al., 2011 | Randomized | Open-label | Reporting properly observed and complete | None | It is a single center study largely conducted in a medical ICU; underpowered to detect samlet differences in VFDs or to determine whether small differences in mortality or other clinical outcomes between the 2 groups are significant; patients with GI hemorrhage were underrepresented due to clinicians' reluctance to enterally feed these patients early in their ICU course |




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Fig. 1:** Pooled odds ratio with 95% confidence interval (CI) for in-hospital mortality with hypocaloric and hyperproteic vs normocaloric enteral feeding. The random effects model was used




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias!
(G) Other bias

**Fig. 2:** The pooled mean difference with 95% confidence interval (CI) for days in mechanical ventilation (MVD) with hypocaloric/hyperproteic vs normocaloric enteral feeding. The random effects model was used

odds ratios (ORs) from 0.75, favoring the intervention and 1.75 favoring the control. The ORs for hospital mortality in the study's central estimates ranged from 0.77 to 1.31. Survival was comparable between the two groups, with an equal number of events (139/675 vs 139/677) and an average weighted effect of 0.99 (Fig. 1). Based on the pooled effects, there was insufficient evidence to suggest that the risk of mortality was higher among patients receiving hypocaloric and hyperproteic feeding than in the normocaloric group. Owing to the moderate likelihood of attrition bias and imprecision from at least two of the included studies, the quality of the evidence for this outcome was low.

### *Days in Mechanical Ventilation*

We analyzed four (4) trials that evaluated the days of mechanical ventilation: Mousavian et al. (2020), Rice et al. (2011), Rugeles et al. (2013), and Rugeles et al. (2016). The other two included trials either did not report the number of ventilation days or did not include it as an outcome of the investigation. We found low-statistical heterogeneity ($I^2$ = 0%) between studies. The APACHE scores of the participants were comparable for both intervention groups involving generally well-nourished patients based on BMI (BMI range, 23.7–28.7), a comparable number of male and female participants, and >90% reported ventilator dependence throughout the follow-up period. Based on the pooled effects, there was insufficient evidence to suggest that the number of days of mechanical ventilation was significantly lower in the intervention group than in the control group (Fig. 2). Owing to the risk of bias and imprecision, the quality of evidence for this outcome may be low to moderate.

### *Length of Hospital Stay*

We evaluated three (3) relevant trials for this outcome on hospital length of stay: Arabi et al. (2015), Charles et al. (2014), and Mousavian et al. (2020). Substantial statistical heterogeneity was observed ($I^2$ = 75%). Clinical heterogeneity due to differences in participants (mixed medical and surgical patients), determination of required

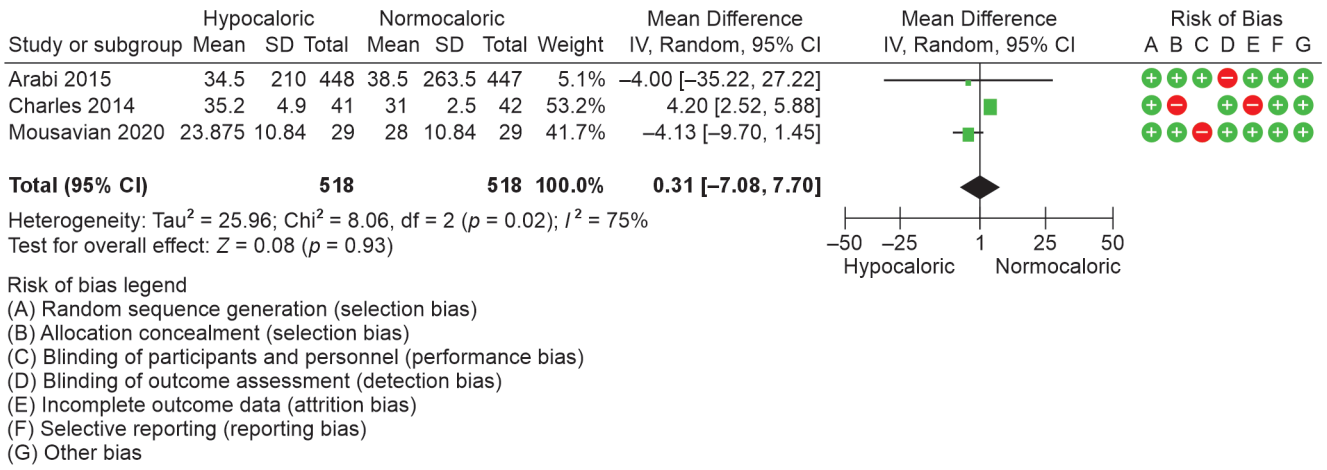



**Fig. 3:** Pooled mean difference with 95% confidence interval (CI) for Length of Hospital Stay (in days) with hypocaloric and hyperproteic vs normocaloric enteral feeding. The random effects model was used

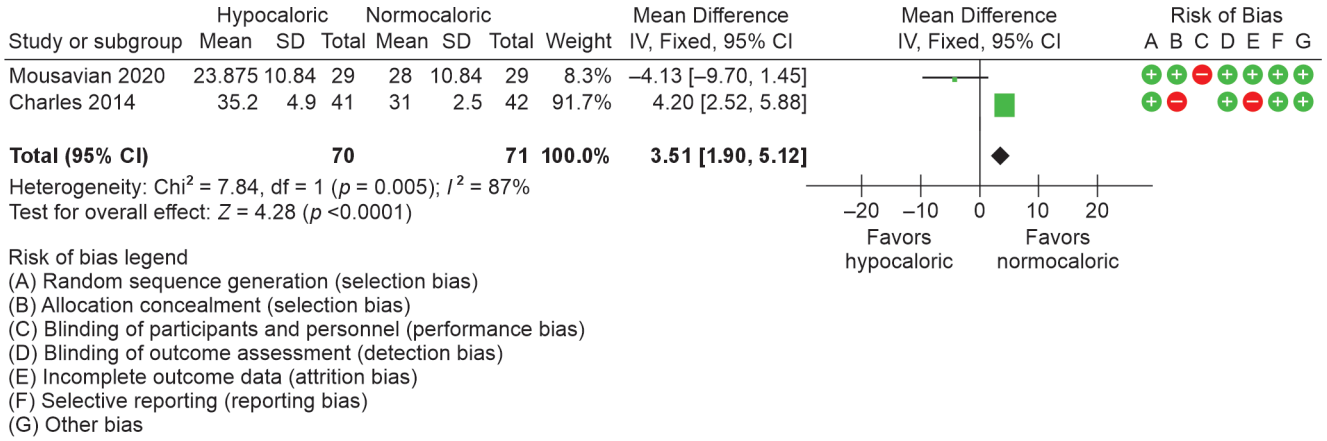



**Fig. 4:** Pooled mean difference with 95% confidence interval (CI) for Length of Hospital Stay (in days) with hypocaloric and hyperproteic vs normocaloric enteral feeding. The random effects model was used

calories per day, and calories received by participants in both the intervention and control groups could have played a key role. Participants who received hypocaloric and hyperproteic nutritional support had a mean length of stay comparable to that of the normocaloric nutritional support group. Based on the pooled effects, there was insufficient evidence to suggest that the mean length of hospital stay in the intervention group was significantly shorter than that of the control group (Fig. 3). The quality of evidence for this outcome was low because of the risks of bias, inconsistency, and imprecision.

A sensitivity analysis was performed to detect the studies that could have influenced the direction of the true effect of the interventions. The study by Mousavian et al. (2020) appeared to be a major contributor to statistical heterogeneity. However, when either the study by Arabi et al. (Fig. 4) or Mousavian et al. (Fig. 5) (lower weight) was removed, both forest plots suggested favorable outcomes for the normocaloric group.

### *Length of ICU Stay*

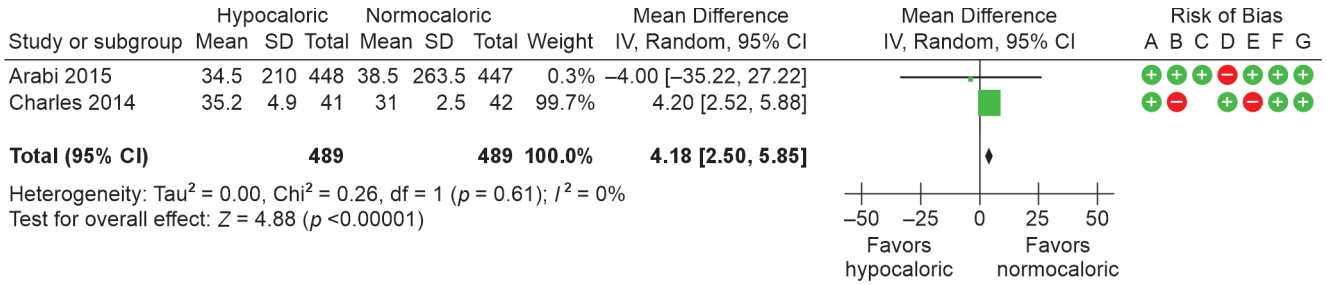
We evaluated four (4) relevant trials for this outcome: Charles et al. (2014), Mousavian et al. (2020), Rugeles et al. (2013), and Rugeles et al. (2016). We found considerable statistical heterogeneity ($I^2 = 94\%$) due to differences in the types of participants and caloric differences between the groups in each trial. Based on the pooled effects, there was insufficient evidence to suggest that the mean length of ICU stay in the intervention group was significantly shorter than that in the control group (Fig. 6). The quality of evidence for this outcome was low because of the risks of bias, inconsistency, and imprecision.

We performed a sensitivity analysis to detect the studies that could have influenced the direction of the true effect of the interventions (Fig. 7). It appears that Charles et al. (2014) had the largest influence on the statistical heterogeneity of the studies involved.

Upon closer scrutiny of the weights of each included study, it was necessary to exclude the trial by Mousavian et al. (2020), as it consistently had the least weight on the intervention effect before and after the sensitivity analysis. And based on the pooled effects, upon exclusion of Mousavian et al. (2020) in the analysis, the mean length of stay in the ICU of the intervention group was lower than the control or normocaloric group by just 0.60 day (Fig. 8).

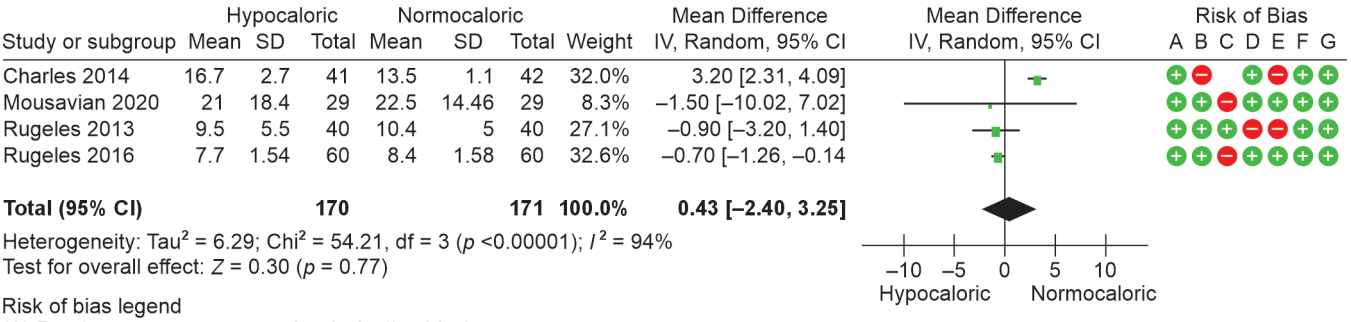
### *Infectious Complications*

We assessed four (4) studies that analyzed infectious complications from any cause: Arabi et al. (2015), Charles et al. (2014), Mousavian et al. (2020), and Rice et al. (2011). Significant heterogeneity was not




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Fig. 5:** Pooled mean difference with 95% confidence interval (CI) for Length of Hospital Stay (in days) with hypocaloric and hyperproteic vs normocaloric enteral feeding. The random effects model was used




Risk of bias legend
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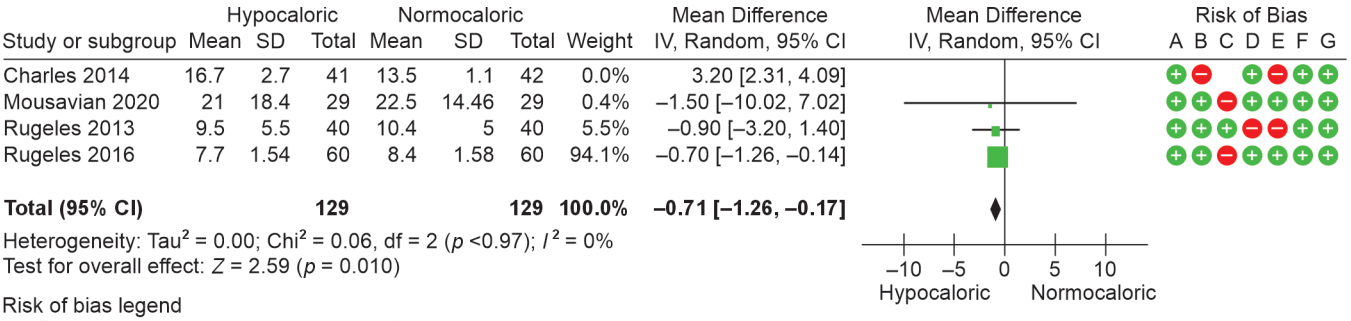
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Fig. 6:** Pooled mean difference with 95% confidence interval (CI) for Length of ICU Stay (in days) with hypocaloric and hyperproteic vs normocaloric enteral feeding. The random effects model was used




Risk of bias legend
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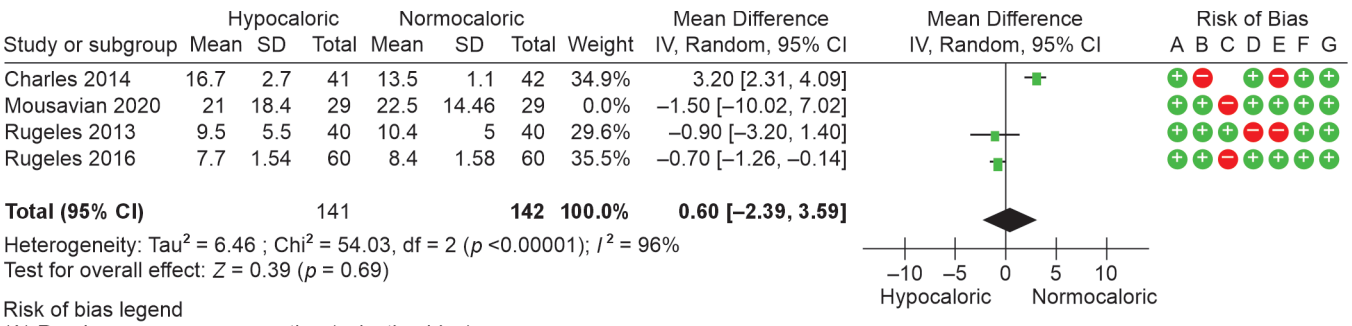
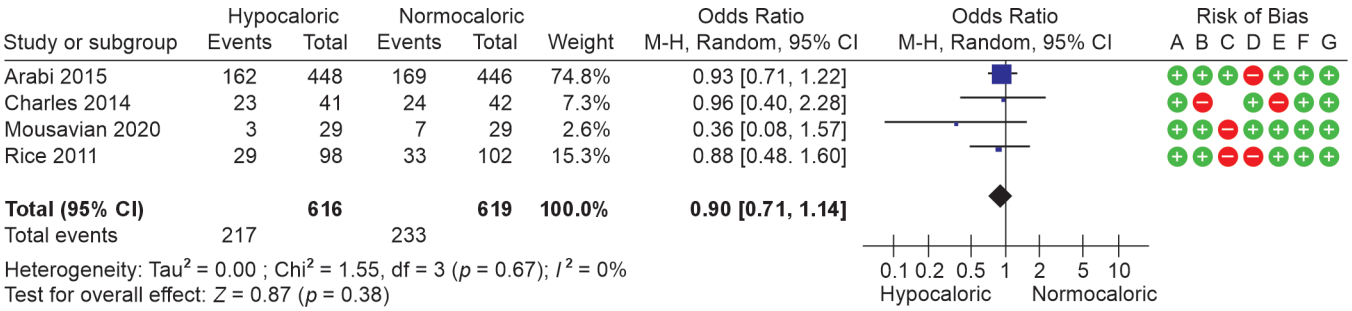
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Fig. 7:** Forest plot of comparison: Hypocaloric vs Normocaloric, outcome ICU LOS




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Fig. 8:** Forest plot of comparison: Hypocaloric vs Normocaloric, outcome ICU LOS




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

**Fig. 9:** Pooled odds ratio with 95% confidence interval (CI) for Infectious complications with hypocaloric and hyperproteic vs normocaloric enteral feeding. The random effects model was used

observed ($I^2$ = 0%). The central estimate of risk ratios for infectious complications in the individual studies ranged from 0.71 to 1.14. Two hundred seventeen (217) participants in the hypocaloric/hyperproteic nutrition group and two hundred thirty-three (233) participants in the control intervention group developed infectious complications of various causes. The control group had a 10% higher risk of developing infection. Based on the overall pooled effects ($p$ = 0.38), there was insufficient evidence to suggest that the number of infectious complications in the intervention group was significantly lower than those in the control and normocaloric groups (Fig. 9). The overall quality of evidence for this outcome was also low considering the risks of bias, inconsistency, and imprecision.

## Discussion

This systematic review presents a comprehensive analysis of several studies comparing the outcomes of hypocaloric/hyperproteic enteral feeding to normocaloric feeding in critically ill patients. The included studies varied in design, patient populations, and nutritional interventions, contributing to a complex understanding of the topic. Notably, higher protein intake may be a fundamental target in critically ill patients regardless of caloric delivery.[4,14–18]

The general findings of this systematic literature review indicated that hypocaloric or hyperproteic intake did not improve the outcomes. However, it is important to note that the evidence for these outcomes was of low quality due to various factors, such as the risk of bias, inconsistency, imprecision, and clinical heterogeneity (diagnosis, severity, dose of EN, protocols, and feeding interruptions). These factors make it difficult to generalize the conclusions to all types of patients in the ICU.

In recent years, guidelines have highlighted the importance of prioritizing adequate nutrition for critically ill patients, owing to their increased risk of malnutrition. Numerous studies, conducted since the early 2000s, have explored the relationship between calorie intake and clinical outcomes. One study found no significant association between caloric intake and hospital mortality rates among critically ill adult patients. However, it concluded that lower calorie intake is associated with a lower risk of bloodstream infections and incident renal replacement therapy.[5] Another study also demonstrated that hypocaloric feeding combined with high protein intake was associated with a significant reduction in mortality compared with normocaloric feeding in the acute phase of critical illness.[2] A meta-analysis conducted in 2014, which included four randomized controlled trials, found that overall mortality was

significantly lower in underfed patients who received ≥33.3% of their target caloric requirement than in those receiving >66.6%.[19] However, a more recent study in 2021 which compared hypocaloric and isocaloric enteral feeding with varying protein contents using trial sequential analysis, showed no survival benefits.[20] There were no restrictions on protein delivery in the study. A trial sequential analysis performed on studies with a low risk of bias, on the same number of proteins, and on different amounts of proteins did not change the results. A similar meta-analysis also showed no difference in the risk of acquired infections, ventilator-free days, mortality, or length of stay in the ICU.[21] However, another meta-analysis suggested that higher caloric intake might not improve outcomes and could potentially lead to increased complications.[22] Similarly, the primary outcome analysis in our study revealed mixed findings on mortality and related outcomes. While some of the included studies showed no significant differences between the hypocaloric and normocaloric groups, others hinted at potential trends favoring only one group.

Interestingly, a recent real-world study that compared hypocaloric feeding to normocaloric feeding after day 3 showed differences in the incidence of nosocomial infection, hyperglycemic events, days of mechanical ventilation, and length of stay in the ICU but no significant difference in mortality. It recommends providing only 30–70% of the energy expenditure in the early phase of illness to avoid overfeeding.[23] A more recent meta-analysis compared hypocaloric feeding of 20 kcal/kg/day (70% of the requirement) with only 1 gm/kg/day of protein vs standard feeding.[24] It primarily studied physical impairment parameters, such as quality of life, physical function, and activities of daily living. While most of the physical impairment variables were not affected in the hypocaloric group, increasing the protein content to >1 gm/kg/day can attenuate complications.[24]

Overall, the lack of a consistent mortality trend suggests the need for further investigation with potentially larger sample sizes to detect meaningful differences. Variability in the results highlighted the complex nature of critical care outcomes and underscored the importance of considering multiple endpoints or prognostic parameters, such as physical functions or impairments, instead of just hard endpoints, such as mortality.

## Conclusion

The meta-analysis concluded that the hypocaloric and hyperproteic groups did not provide significant benefits or harm compared with the control group. While there was some trend favoring normocaloric feeding in the length of hospital stay or shorter ICU stay in the hypocaloric/hyperproteic group, the overall evidence was limited by methodological challenges, clinical heterogeneity, and potential biases. These findings underscore the need for larger, well-designed trials to elucidate the impact of hypocaloric and hyperproteic enteral feeding on critical care outcomes, specifically in relation to the exact dose of macronutrients, nutritional status, and specific comorbidities. The use of this nutritional strategy should be approached cautiously considering patient-specific factors and the evolving landscape of critical care research.

## Orcid

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# Appendix A

## Definition of Terms

The acute phase of critical care illness refers to the first 7 days of ICU admission: acute early phase (days 1–2), acute late phase (days 3–7).

Hypocaloric feeding refers to <70% of the required daily energy requirement, regardless of the protein content (ESPEN).

Normocaloric feeding refers to >70% of the required daily energy requirement, regardless of the protein content (ESPEN).

Hyperproteic feeding refers to protein content in feeding above 1.2 gm/kg/day (ESPEN) or above 20% of the total required calories per day.

# Appendix B

## Abbreviations:

ICU – Intensive care unit.

LOS – Length of stay.

MVD – Days in mechanical ventilation.

ESPEN – European Society of Enteral and Parenteral Nutrition.

PhilsPen – Philippine Society of Enteral and Parenteral Nutrition.

SCCM – Society of Critical Care Medicine.

RCT – Randomized Controlled Trial.

EN – enteral nutrition.

TPN – total parenteral nutrition.

BMI – body mass index.

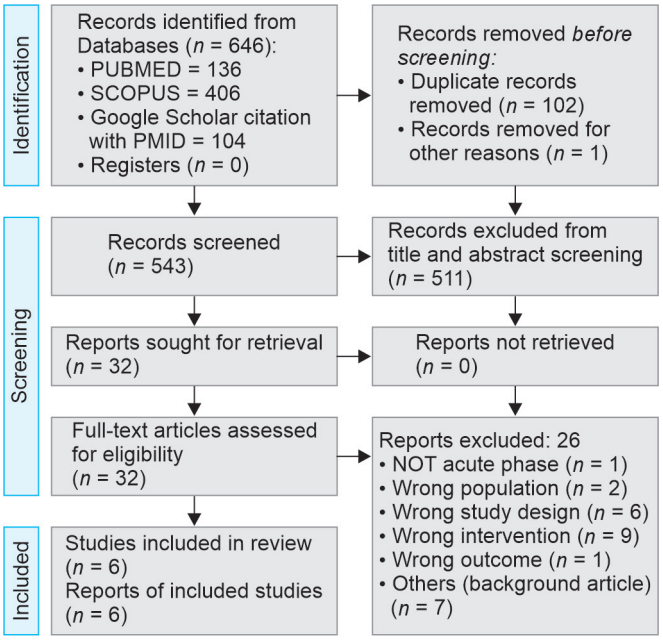
APACHE – Acute physiology, age, and chronic health evaluation.

SOFA – Sequential Organ Failure Assessment.

ASPEN – American Society of Enteral and Parenteral Nutrition.

# Appendix C

**Flowchart:** PRISMA flow diagram for the systematic review



## Appendix D

### UP Manila Research Grants Administration Office (RGAO) Certificate of Registration

UNIVERSITY OF THE PHILIPPINES MANILA
Research Grants Administration Office
G/F Room 111 National Institutes of Health Building, UP Manila, 623 Pedro Gil St., Ermita, Manila 1000, Philippines
Tel: (632) 85672054 • Email: rgao@post.upm.edu.ph

**CERTIFICATE OF REGISTRATION**

| | |
|---|---|
| Research Title | The Impact on patient outcomes of hypocaloric and high-protein enteral feeding vs isocaloric feeding in the acute early phase of critical illness among mechanically-ventilated adult patients: A Systematic Review with meta analysis |
| Principal Investigator | Chito C. Permejo, MD |
| Co-investigator(s) | Teresita Joy Evangelista, MD, MHA |
| Status at Time of Registration | Ongoing |
| Date of Registration | May 30, 2022 |
| RGAO Reference No. | RGAO-2022-0554<br><br>Note: For ease of identification, please use this assigned RGAO Reference Number for all communications with RGAO that is related to this research. |

This is to certify that the abovementioned research is registered with the Research Grants Administration Office for records purposes. However, this does not equal to nor guarantee technical and/or ethics review approval.

**MARK ANTHONY S. SANDOVAL, MD**
Head, Research Grants Administration Office
Office of the Vice Chancellor for Research, UP Manila

## Appendix E

### PROSPERO Registration

NIHR | National Institute for Health and Care Research

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|---|---|---|---|
| CRD42021283247 | The impact on patient outcomes of early hypocaloric and hyperproteic/high-protein (intervention) vs normocaloric (standard care) enteral feeding in the early acute phase of critical illness among patients admitted in the ICU. | Registered | 22/12/2021 |