META-ANALYSIS

Effect of Adopting Low Calories on Patients' Vital Signs in The Nutritional Support of Critically Ill Patients in the ICU: A Systematic Review and Network Meta-Analysis

Qidong Jiang, MM; Lingxiao Duan, MM

ABSTRACT

Background • Feeding critically ill persons in Intensive Care Units (ICUs) is challenging as the nutritional substances pose severe health outcomes or can improve their well-being and length of stay (LOS) in the hospital. Our main objective is to investigate the effects of adopting low caloric intake among patients with vital signs in the nutritional support of critically ill patients in ICUs, focusing on reducing mortality rates and length of stay (LOS) in hospitals.

Method • The initial literature search was performed in PubMed, the Cochrane Library of Trials, and MEDLINE. The network meta-analysis was performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two independent reviewers were assigned data selection and extraction roles. Our study mainly included randomised controlled trials (RCTs) whose titles and abstracts were screened, after which duplicates were excluded. The remaining eligible studies were subjected to full-text analysis to identify data related to the topic of the present study. Analyses were performed using the Cochrane Risk of Bias tool, R software and MS Excel.

Results • Twenty-two studies (involving 9 539 participants) met the inclusion criteria and were subjected to the network meta-analysis. In mortality rates, the greatest rank observed corresponded to a reduction of 71%. The regression of the effects of low caloric intake explained a 5.29% variation in LOS. A weak positive correlation was found between LOS and low caloric intake among critically ill patients in ICUs. Thus, Low caloric intake decreased mortality rates and lowered LOS.

Conclusions • Our study found that low caloric intake reduces mortality rate and hospital LOS among critically ill patients. Secondary outcomes include nosocomial infection, clinical outcomes, functions, digestive infections, improved quality of life, resulting survival rates, ventilator days, bacteremia, blood glucose levels, diarrhoea, and tube replacement. Our findings have clinical implications for clinicians in the ICU, who should consider developing individualised nutritional plans for critically ill patients. Moreover, regular monitoring of nutritional intake and response is crucial. Healthcare providers should closely monitor patients' nutritional status, vital signs, and clinical outcomes. (*Altern Ther Health Med.* [E-pub ahead of print.])

Qidong Jiang, MM; LingxiaoDuan, MM; Intensive Care Unit, The Affiliated Hospital of Southwest Medical University, Luzhou City, Sichuan Province, China.

Corresponding author: Lingxiao Duan, MM
E-mail: 18367796@qq.com

INTRODUCTION

Nutritional needs in intensive care units (ICUs) are essential because nutrition is integral to the therapeutic process.[1,2] Providing appropriate nutritional support to critically ill patients can improve their metabolic function, reduce hospital and ICU lengths of stay, enhance the quality of life, and lower morbidity rates.[3] Critically ill patients with indications of nutritional deficits often experience catabolic stress and systemic inflammatory responses, leading to common complications such as multi-organ failure, infectious morbidity, nosocomial infections, and prolonged hospitalisation.[1,4,5] Furthermore, inadequate feeding can exacerbate vulnerability to infections and other diseases. Unlike parenteral feeding, enteral feeding is preferred as it delivers nutrients directly to the gastrointestinal tract, resulting in improved patient outcomes and shorter hospital stays.

Despite studies emphasising the importance of meeting the nutritional needs of critically ill patients in ICUs, the impact of low-caloric intake on patients with vital signs remains unclear.[6] Low and high caloric intake regimens have been associated with potential side effects in critically ill patients. The effects of adopting low-calorie diets among critically ill ICU patients remain elusive. However, existing literature hints at the potential benefits of low caloric intake, including reduced morbidity and mortality rates.[5]

According to Indrio et al.,[7] enteral feeding is a medical nutrition therapy that directly delivers essential nutrients

into the gastrointestinal tract. This method is typically implemented through specialised tubes, which can be inserted through different routes, including the nose, mouth, or abdominal wall, to reach the stomach or small intestine.[8] These tubes allow for the controlled administration of a well-balanced liquid nutritional formula that contains essential macronutrients (proteins, carbohydrates, and fats), micronutrients (vitamins and minerals), and fluids. Enteral feeding ensures that patients receive vital nourishment, even when they cannot consume food orally due to their medical condition or treatment requirements.[7]

Prest et al.[9] suggested that enteral feeding has become the preferred method for delivering nutrition to critically ill patients in the intensive care unit (ICU). Several factors contribute to the widespread adoption of enteral feeding in this context. Firstly, it is favoured for its ability to maintain the integrity and function of the gastrointestinal tract. This preservation of the digestive system is crucial, as it plays a pivotal role in nutrient absorption, immune function, and the maintenance of gut barrier integrity.[10] Moreover, enteral feeding allows for precise control over the composition and rate of nutrient delivery. Healthcare professionals can tailor the nutritional formula to meet each patient's needs, ensuring they receive adequate proteins, carbohydrates, fats, vitamins, and minerals. This individualised approach is critical in ICU care, where patients' nutritional requirements vary significantly.

Additionally, studies consistently show that enteral feeding is associated with a lower risk of complications than alternative methods like parenteral feeding (intravenous nutrient administration).[11-13] Reduced complications, such as a lower likelihood of infections and a shorter duration of hospitalisation, contribute to the preference for enteral feeding. Beyond meeting nutritional needs, enteral feeding aligns with the broader goal of promoting the overall well-being of critically ill patients. By supporting the natural digestive process and maintaining gut function, it can contribute to better outcomes, shorter recovery times, and improved quality of life for patients in the ICU.

Our Systematic Review and Network Meta-Analysis will comprehensively assess and synthesise existing literature on the effects of low-caloric intake among critically ill patients in ICUs with a focus on enteral feeding. Through a systematic review of relevant studies and network meta-analysis techniques, such as bubble plots, forest plots and regression, we will evaluate the impact of low-caloric intake on mortality rates, length of stay, and quality of life. The findings will provide valuable insights into evidence-based practices for addressing critically ill patients' nutritional needs and guide clinical decision-making.

Rationale and Objectives

The rationale behind this study stems from the adverse effects of hypocaloric and hypercaloric intake on critically ill patients requiring vital nutritional support. The study aims to provide robust evidence that can inform nutritional decision-making and improve the clinical outcomes of critically ill patients in ICUs.

The following specific objectives were formulated: (1) To determine whether adopting a low-calorie nutritional approach for critically ill patients with vital signs for nutrition in ICUs reduces mortality rates compared to standard nutritional care; (2) To investigate the effect of low-caloric intake on the length of stay in hospitals and ICUs among critically ill patients, comparing patients on low-calorie enteral feeding to those on standard nutritional regimens; (3) To measure and compare the quality of life among critically ill patients who receive low-calorie nutritional support to those who receive standard nutritional care, considering parameters such as physical well-being, psychological health, and overall satisfaction with care.

METHODS

Registration and Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol defined the rationale of the present study, including the analysis methods and hypotheses.[14,15] The PRISMA checklist dispenses the order of the present study (see Table 1). Our study, with the DOI number http://dx.doi.org/10.37766/inplasy2022.12.0052, was registered on 20th February 2023 with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY). The registration serves to enhance transparency and credibility in our research. The decision to register the study was driven by the need to minimise publication bias and establish a clear record of our research objectives, methods, and analysis plan. This proactive approach ensures that our study is not influenced by post hoc modifications or selective outcomes reporting, aligning with scientific rigour and integrity principles.

In the registration, we provided comprehensive details about the study's scope, objectives, eligibility criteria, data extraction methods, statistical analysis plan, and anticipated outcomes. This level of detail is vital for maintaining methodological consistency and minimising the risk of bias during the review process. Additionally, our study registration closely adheres to the PRISMA protocol, a recognised systematic review and meta-analysis guideline. PRISMA's structured framework ensures transparency and a systematic approach to study selection, data extraction, and meta-analysis, contributing to the rigour and reproducibility of our research

Search strategy

An initial literature search was performed in three electronic databases – Cochrane Library of Trials, PubMed, MEDLINE, and EMBASE for eligible studies. These databases were searched from 2007 to 2023 for relevant publications. Medical subject terms (MeSH) for keywords used in the literature search were combined using Boolean operators "OR" and "AND". The Boolean operator "OR" was used to combine keywords with similar meanings, whereas the Boolean operator "AND" was used to combine words with dissimilar meanings. The following keywords were used in

Table 1. A Prisma Checklist For The Network Meta-Analysis

Section and Topic	Item#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2030 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses) and, if not, the methods used to decide which results to collect.	10
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	10-17
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	N/A
Effect measures	12	Specify for each outcome the effect measure (s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	18
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	18
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics or data conventions.	18
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	18
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	18
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	18
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study section	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	19
	16b	Cite studies that might appear to meet the inclusion criteria but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	19-20
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	21
Results of individual studies	19	For all outcomes, present for each study. (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	22
Section and Topic	Item #	Checklist item	Location where item is reported
Studies			
Results of synthesis	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23
	23b	Discuss any limitations of the evidence included in the review.	23-33
	23c	Discuss any limitations of the review processes used.	34
	23d	Discuss implications of the results for practice, policy, and future research.	35
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary appendix

the initial literature search: Aged, Duodenum, Enteral Nutrition/methods*, Female, Humans, Intensive Care Units*, Male, Prospective Studies, Stomach, Adult "OR" Aged, Blood Glucose/analysis, Caloric Restriction*, Critical Illness/mortality, Critical Illness/therapy*, Drug Monitoring, Energy Intake, Enteral Nutrition, Female, Hospitals, University, Humans, Insulin / therapeutic use*, Intensive Care Units, Kaplan-Meier Estimate, Length of Stay, Male, (Middle Aged, "AND" (Respiration, "AND" Artificial / statistics & numerical data[MeSH Terms]))

Eligibility Criteria

Our inclusion criteria involved studies that reported low caloric intake among critically ill patients in ICUs, with clear definitions of low caloric intake, either through specified calorie thresholds or relative reductions compared to standard diets. Only publications with in-depth statistical analysis were included, including percentages of intervention outcomes, variability measures (data range or standard deviation), and central tendency measures (medians or means). Preference was given to randomised controlled trials (RCTs) as they provide robust evidence. Exclusion criteria encompassed non-English publications, studies primarily involving non-critically ill patients or non-ICU settings, those lacking sufficient data on low caloric intake, and studies without adequate statistical analysis. These criteria were applied to ensure the selection of relevant studies meeting the specific objectives of our systematic review and network meta-analysis.

Data Extraction

Two independent reviewers were assigned data extraction roles. They screened the titles and abstracts of potential studies in the electronic databases for eligibility, after which they performed a full-text analysis of the potential studies. Any disagreements between the two reviewers were resolved by consensus. Data were extracted from studies reporting the effect of low caloric intake among critically ill patients in ICUs. At the same time, studies comparing these outcomes with high caloric intake or control groups were considered. We extracted data on the author's surname, year of publication, study design, country of origin, sample sizes, baseline characteristics of patients, intervention, controls and critical outcomes.

Outcomes

The mortality rate of low caloric intake was the primary outcome, and the LOS in ICUs was the primary outcome and the mortality rate. The length of hospital stay was measured in days. The mortality rate was obtained through a percentage of the deceased against the total number of participants in the study. Percentages of the deaths reported by the individual studies were reported. After the meta-analysis of the studies for mortality rates and LOS, an analysis was performed for additional findings in the studies and reported as secondary outcomes. They include nosocomial infection, clinical outcomes, functions, digestive infections, improved quality of life, resulting survival rates, ventilator days, bacteremia, blood glucose levels, diarrhoea, and tube replacement.

Quality Assessment

Our study adopted the Cochrane Risk of Bias Tool (The Cochrane Collaboration, Oxford, England) to assess the quality of the selected publications based on unclear risk of bias, low risk of bias and high risk of bias. The risk of bias was assessed based on random sequence generation, allocation concealment, blinding of participants and personnel, attrition bias, reporting bias and other biases.

Data synthesis

Our study used R studio software (version 4.1.3) to construct the corresponding plots, particularly the Ggplot, geom_point(), meta, metafor, rmeta, and epiR. Also, we performed a heterogeneity test using the I^2 statistic (Higgins et al., 2003; Petitti, 2001 and Hardy et al., 1998) to establish the genuine differences in the outcomes reported by the individual studies (I^2 < 45% = low, 45% ≤ I^2 ≤ 75% = moderate, I^2 > 75% = high). A meta-regression on LOS was performed using Microsoft Excel, where Pearson correlation and the ANOVA test were used to measure the correlation of two factors and the statistical significance. The analyses were visualised using a bubble graph, a funnel plot, tables of figures or data, and a box plot. A discussion and conclusions on the effect of adopting low caloric intake were based on the outcomes of this analysis.

Characteristics of Included Studies

The two independent reviewers extracted the following data from the selected studies: study ID and years of publication, study design, country of origin, and participant features like mean age, sex, intervention, and control, alongside the key observations from the respective studies (see Table 2 and Figure 1).

Statistical Analysis

LOS and mortality rates will be meta-analysed to show the effect of low caloric intake. A meta-analysis was performed

Figure 1. A network plot of the effects reported by the included studies

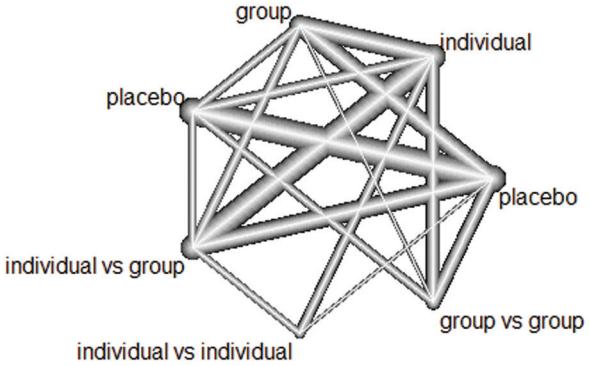


Table 2. Characteristics of Included Studies

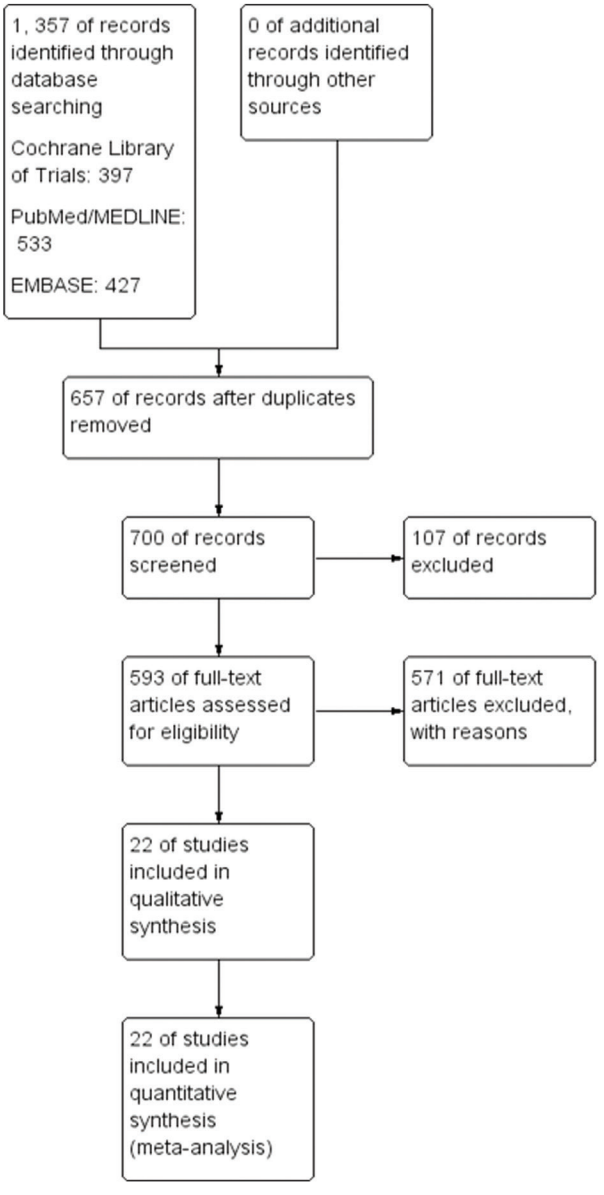
Study ID, Year of publication	Study Design	Country of origin	Participant (n), sex, %), APACHE MEAN	Mean Age	Intervention (daily calorific intake	Control (daily calorific intake)	Duration of intervention	Key outcomes
Nguyen et al., 2007	A randomized, controlled, double-blind trial	Australia	75(75% males) IG: 23 CG: 22.26	IG: 50.9 years CG: 52 years	Combined pharmacologic therapy (metoclopramide+ erythromycin higher than calories	Significantly lower pharmacological intervention (erythromycin) than caloric intake	7 days	A significant difference in LOS between IG and CG was not reported. Water diarrhea in the IG surpassed CG, without enteric infections.13% and 17% mortality rates in the IC and CG groups, respectively.
Desachy et al., 2008	Open prospective, randomized study	France	100(69% males) IG: 82 CG: 18	IG: 64 years CG: 58 years	Gradual feeding: (76%) of optimal calorie (1,297±331 kilocalories)	Immediate feeding: 95% of optimal calories (1,715±331 kilocalories)	120±48 hours and a 7-day patient follow-up	The frequency of severe adverse effects is similar in the IG and CG 11% and 11% mortality rate in the IC and Cg groups, respectively.
HSU et al., 2009	A prospective, randomized clinical study	Taiwan	121 (70.2% males) IG: 20.5 CG: 20.3	IG: 70 years CG: 67.9 years	ND: 1,658± 118 kcal; 27.1 ±7.6 kcal/kg/day protein consumption: 1.11±0.31 g/kg/day	NG: 1,426±110 kcal; 23.5 ±8.8 kcal/kg/day	Mean study period: 11 days	Nutritional goals were achieved earlier in the ND group than NC group. The mortality rate was found not to differ significantly between the two groups.
White et al., 2009	A prospective randomized study	Australia	104 (50% males) IG: 30 CG: 24.5	IG: 50 years CG: 54 years	Post-pyloric feeding: 1,296 kcal, 88.5% caloric	Gastric feeding: 1,515 kcal, 95% caloric	3 to 4 days	Concerning overall complications and nutritional outcome, post-pyloric and gastric feeding did not report significant differences. 3% and 5% mortality rates in the IC and CG groups, respectively.
Arabi et al., 2011	2*2 factional randomized, controlled design	Saudi Arabia	240(68.3% males) IG: 25.2 CG: 25.3	IG: 50.3 years CG: 5.19 years	Permissive underfeeding: 59% of calorie requirement (1, 066±306 kcal), 13.9 kcal/kg/day	Target feeding: 71.4% of calorie requirements (1,251±432 kcal), 16.4 kcal/kg/day	Up to ICU discharge	Unlike target feeding, permissive feeding among critically-ill patients could result in low mortality rates. 18% and 23% mortality rates in the IC and Cg groups, respectively.
Charles et al., 2014	RCT	United States of America	83 (71% males) IG: 23.4 CG: 27.7	IG: 52.2 years CG: 58.6 years	Hypocaloric feeding: approximately 50% of the requirement; 12.5 to 15kcal/kg/day (982±61 kcal; 12.3±0.7 kcal/kg/day)	Eucaloric feeding: approximately 25 to 30 kcal/kg/day (1,338±92kcal; 17.1±1.1 kcal/kg/day	N/A	Calorie intake across a wide range did not result in major outcomes, especially infection. 7.3% and 9.5% mortality rates in the IC and CG groups, respectively
Braunschweig et al., 2015	Prospective randomized trial	United States of America	78 (51.2 % males) IG:23.4 CG: 27.7	IG: 52.5 years CG: 58.6 years	<75% of intensive medical nutrition supplied (1,798±509 kcal; 25.4±6.6 kcal/kg/day). 84.7% of energy needs supply	Standard nutrition: 1,221±423 kcal; 16.6±5.6 kcal/kg/day. 55.4% of energy requirements supplied	Up to discharge	Intensive medical, nutritional supply of low calories for patients with acute lung injury increased mortality rates of 40% and 16% in the IG and CG, respectively.
Arabi et al., 2015	RCT	Canada	894 (64.2% males) IG: 21.	IG: 50.2 years CG: 50.9 years	Permissive feeding: at the supply of 40% to 60% of caloric needs: 835±297 kcal, which is 46% of the needs	Standard feeding: 70% to 100% of the caloric needs: 1,299±467 kcal, which is 71% of the caloric needs	Up to 14 days	A low supply of non-protein calories did not result in low mortality rates.
Doig et al., 2015	A randomized, multicenter, single-blind clinical trial	Australia	331 (58.6% males) IG: 18 CG: 18	1G: 59 years CG: 61 years	Protocolized caloric restriction: 20 kcal/h for ≥2 days, after which an adjustment would be made according to serum phosphate	Standard care: 68.5 kcal/h mean caloric intake	≤4 days	Caloric restriction is ideal for therapeutic outcomes among critically ill adults with the re-feeding syndrome. Safety concerns were not identified in the study.
Kearns et al., 2000		A prospective, randomized, controlled trial	44 (68% males) IG: 22 CG: 22	1G: 54 years CG: 49 years	A supply of 69± 7 caloric needs: 1,157±86 kcal; 18±1 kcal/kg/day	A supply of 47 ± 7 caloric needs: 812 ±122 kcal/kg/day	7 to 10 days	Unclear difference between VAP's incidence in SI when G enteral nutrition was applied. Mortality rated did not differ in the IG and CG.
Acosta-Escribano et al., 2010	A prospective, open-label, randomized study	Spain	104 (86.5% males) IG: 16 CG: 18	IG: 35 years CG: 41 years	92% of the feeding volume	Supply of 84% of caloric requirements	N/A	Low-calorie supply improved nutritional deficiency and reduced the incidence of late pneumonia. The mortality rate in the IG and CG was 8 and 10, respectively.
Singer et al., 2011	Prospective, randomized single-center, pilot clinical trial	Israel	130 (58% males) IG: 22.1 CG: 22.4	IG: 59 years CG:62 years	Tight caloric consumption (2,086±467 kcal via the indirect calorimetry and a protein intake of 0.95 g/kg/day	Standard caloric consumption (25 kcal/kg/day, 1,489±356 kcal) and a protein intake of 0.68 g/kg/day	Unclear until the 14th day to discharge	Low calorific consumption was associated with low hospital mortality. Low hospital mortality was reported: 32.3% and 47.7% in the IG and CG, respectively.
Rice et al., 2011	A randomized, open-label study	United States of America	200 (100% males)		Tropical feeding: 98	Full feeding: 102		22.4% and 19.6 % mortality rates in the IG and CG, respectively.
Rice et al., 2012	Randomized open-label multicenter trial	United States of America	1,000(100% males)	NA	Tropical feeding: 508	Full feeding: 492	28 days	23.2 % and 22.2% mortality rates in the IC and CG groups, respectively.
Montecalvo et al., 1992	Randomized prospective trial	United States of America	38	NA	19	19	2 days	11.2% and 15.9% mortality rates in the IC and CG groups respectively.
Montejo et al., 2010	Open prospective, randomized study	Spain	104	≥15 years	157	165	3 days	Reduced mortality rates between the intervention and control groups 17% and 21% respectively.
Huang et al., 2012	Prospective, randomized clinical study	Taiwan	101	NA	51	50	21 Days	A mortality rate of 30% and 49.3% were reported in the IG and CG, respectively.
Reignier et al., 2013	Randomized, noninferiority open-label multicenter trial	France	449	NA	38/227	35/222	4 days	A low mortality rate in the IG and CG group, 6.7% and 7.1%, respectively was reported.
Peake et al., 2014	Prospective randomized, double-blind parallel- group, multicenter study	Australia	112	NA	57	55	NA	The IG and CG reported a hospital mortality rate of 20% and 37%.
Reignier et al., 2021	Randomized, controlled, multicenter, open-label, parallel-group trial	France	34	NA	17: Calorie-protein restriction (6kcal/kg/day to 0.2-0.4 kcal/kg/day)	17: standard calorie-protein target of 25 kcal/kg/day	7 days	Secondary clinical outcomes reported include nosocomial, functional and clinical outcome
Reignier et al., 2018	Randomized, controlled, multicenter, open-label, parallel-group trial	France	2,797	≥18 years	1,202	1,208	7 days	Digestive complications
Harvey et al., 2016	A multicenter, randomized controlled trial	United Kingdom	2,400	NA	1,183 of 1,200 low-caloric nutritional support	1.951 of 1,200 parenteral nutritional support	NA	Improved quality of life and high rates of survival

Abbreviations: ICU, Intensive Care Unit; IG, Intervention Group; CG, Control Group; ND, Nasoduodenal feeding; RCT, Randomised controlled trial; NG, Nasogastric feeding.

Table 3. Random OR league table of the effects of low calories

Acute lung injuries	0.364 (0.033, 4.038)	0.057 (0.001, 2.166)	0.164 (0.005, 5.962)	0.466 (0.022, 9.862)	2.084 (0.101, 43.082)	0.912 (0.045, 21.037)	0.048 (0.002, 1.008)	0.832 (0.106, 6.537)	0.566 (0.037, 8.565)	1.386 (0.032, 59.782)	4.600 (0.251, 84.167)	0.026 (0.001, 0.461)	0.462 (0.059, 3.647)	1.587 (0.064, 39.323)	3.996 (0.219, 72.792)	0.096 (0.009, 1.079)	0.012 (0.001, 0.256)	0.023 (0.001, 0.493)
2.750 (0.248, 30.530)	Adverse effects	0.156 (0.006, 4.076)	0.452 (0.018, 11.156)	1.281 (0.096, 17.051)	5.732 (0.510, 64.444)	2.507 (0.170, 36.918)	0.133 (0.010, 1.739)	2.289 (0.593, 8.827)	1.556 (0.175, 13.807)	3.811 (0.127, 114.080)	12.648 (1.108, 144.359)	0.070 (0.006, 0.787)	1.270 (0.351, 4.593)	4.363 (0.273, 69.819)	10.987 (0.968, 124.749)	0.264 (0.061, 1.143)	0.034 (0.003, 0.388)	0.065 (0.005, 0.851)
17.588 (0.462, 669.881)	6.396 (0.245, 166.734)	Clinical functions	2.889 (0.197, 42.258)	8.196 (0.194, 346.887)	36.661 (0.862, 1559.936)	16.035 (0.353, 728.436)	0.849 (0.020, 35.545)	14.639 (0.683, 313.563)	9.949 (0.307, 322.273)	24.376 (1.328, 447.466)	80.899 (2.087, 3135.989)	0.450 (0.012, 17.177)	8.125 (0.406, 162.666)	27.905 (0.579, 1344.665)	70.274 (1.819, 2714.600)	1.690 (0.065, 44.199)	0.218 (0.005, 9.117)	0.413 (0.010, 17.364)
6.088 (0.168, 220.964)	2.214 (0.096, 54.686)	0.346 (0.024, 5.064)	Clinical outcomes	2.837 (0.070, 114.572)	12.690 (0.313, 515.275)	5.551 (0.128, 240.808)	0.294 (0.007, 11.739)	5.067 (0.251, 102.483)	3.444 (0.112, 106.059)	8.438 (0.488, 145.780)	28.003 (0.758, 1034.631)	0.156 (0.004, 5.667)	2.813 (0.149, 53.091)	9.659 (0.210, 444.878)	24.327 (0.661, 895.605)	0.585 (0.024, 14.498)	0.075 (0.002, 3.011)	0.143 (0.004, 5.734)
2.146 (0.101, 45.404)	0.780 (0.059, 10.383)	0.122 (0.003, 5.163)	0.352 (0.009, 14.234)	Digestive complications	4.473 (0.185, 107.921)	1.957 (0.075, 50.973)	0.104 (0.004, 2.452)	1.786 (0.173, 18.465)	1.214 (0.070, 21.130)	2.974 (0.062, 142.039)	9.870 (0.457, 213.257)	0.055 (0.003, 1.165)	0.991 (0.105, 9.372)	3.405 (0.122, 95.031)	8.574 (0.398, 184.491)	0.206 (0.015, 2.755)	0.027 (0.001, 0.629)	0.050 (0.002, 1.199)
0.480 (0.023, 9.916)	0.174 (0.016, 1.962)	0.027 (0.001, 1.161)	0.079 (0.002, 3.200)	0.224 (0.009, 5.395)	Gastric feeding	0.437 (0.017, 11.467)	0.023 (0.001, 0.552)	0.399 (0.041, 3.861)	0.271 (0.015, 4.758)	0.665 (0.014, 31.925)	2.207 (0.104, 46.642)	0.012 (0.001, 0.256)	0.222 (0.023, 2.114)	0.761 (0.027, 21.377)	1.917 (0.091, 40.346)	0.046 (0.004, 0.580)	0.006 (0.000, 0.137)	0.011 (0.000, 0.270)
1.097 (0.048, 25.302)	0.399 (0.027, 5.873)	0.062 (0.001, 2.833)	0.180 (0.004, 7.815)	0.511 (0.020, 13.316)	2.286 (0.087, 59.931)	Hospital mortality	0.053 (0.002, 1.362)	0.913 (0.079, 10.555)	0.620 (0.033, 11.843)	1.520 (0.030, 77.758)	5.045 (0.214, 118.771)	0.028 (0.001, 0.649)	0.507 (0.048, 5.380)	1.740 (0.058, 52.589)	4.382 (0.187, 102.760)	0.105 (0.007, 1.558)	0.014 (0.001, 0.349)	0.026 (0.001, 0.666)
20.718 (0.992, 432.681)	7.535 (0.575, 98.711)	1.178 (0.028, 49.323)	3.403 (0.085, 135.938)	9.655 (0.408, 228.583)	43.185 (1.812, 1028.956)	18.891 (0.734, 486.142)	LOS	17.245 (1.697, 175.248)	11.720 (1.149, 119.498)	28.714 (0.607, 1357.364)	95.297 (4.469, 2032.456)	0.530 (0.025, 11.098)	9.571 (1.031, 88.881)	32.871 (1.192, 906.599)	82.781 (3.898, 1758.119)	1.991 (0.151, 26.188)	0.257 (0.011, 5.995)	0.487 (0.047, 5.049)
1.201 (0.153, 9.436)	0.437 (0.113, 1.685)	0.068 (0.003, 1.463)	0.197 (0.010, 3.991)	0.560 (0.054, 5.789)	.504 (0.259, 24.211)	1.095 (0.095, 12.667)	0.058 (0.006, 0.589)	Mortality	0.680 (0.104, 4.443)	1.665 (0.067, 41.306)	5.526 (0.679, 44.966)	0.031 (0.004, 0.247)	0.555 (0.293, 1.053)	1.906 (0.150, 24.146)	4.801 (0.594, 38.823)	0.115 (0.029, 0.460)	0.015 (0.001, 0.148)	0.028 (0.003, 0.289)
1.768 (0.117, 26.765)	0.643 (0.072, 5.707)	0.101 (0.003, 3.256)	0.290 (0.009, 8.942)	0.824 (0.047, 14.341)	3.685 (0.210, 64.606)	1.612 (0.084, 30.769)	0.085 (0.008, 0.870)	1.471 (0.225, 9.619)	Mortality rates	2.450 (0.066, 90.369)	8.131 (0.525, 126.027)	0.045 (0.003, 0.687)	0.817 (0.140, 4.771)	2.805 (0.136, 57.772)	7.063 (0.458, 108.973)	0.170 (0.019, 1.515)	0.022 (0.001, 0.376)	0.042 (0.004, 0.426)
0.722 (0.017, 31.125)	0.262 (0.009, 7.855)	0.041 (0.002, 0.753)	0.119 (0.007, 2.048)	0.336 (0.007, 16.061)	1.504 (0.031, 72.219)	0.658 (0.013, 33.656)	0.035 (0.001, 1.646)	0.601 (0.024, 14.898)	0.408 (0.011, 15.056)	Nosocomial infections	3.319 (0.076, 145.605)	0.018 (0.000, 0.798)	0.333 (0.014, 7.752)	1.145 (0.021, 62.016)	2.883 (0.066, 126.053)	0.069 (0.002, 2.082)	0.009 (0.000, 0.422)	0.017 (0.000, 0.804)
0.217 (0.012, 3.978)	0.079 (0.007, 0.902)	0.012 (0.000, 0.479)	0.036 (0.001, 1.319)	0.101 (0.005, 2.189)	0.453 (0.021, 9.578)	0.198 (0.008, 4.667)	0.010 (0.000, 0.224)	0.181 (0.022, 1.472)	0.123 (0.008, 1.906)	0.301 (0.007, 13.218)	Nutritional deficiency	0.006 (0.000, 0.103)	0.100 (0.012, 0.818)	0.345 (0.014, 8.720)	0.869 (0.082, 9.216)	0.021 (0.002, 0.241)	0.003 (0.000, 0.057)	0.005 (0.000, 0.109)
39.068 (2.167, 704.156)	14.208 (1.270, 158.872)	2.221 (0.058, 84.758)	6.417 (0.176, 233.341)	18.207 (0.859, 386.063)	81.435 (3.911, 1695.275)	35.620 (1.541, 823.530)	1.886 (0.090, 39.464)	32.515 (4.055, 260.734)	22.100 (1.456, 335.392)	54.141 (1.253, 2339.518)	179.702 (9.739, 3315.952)	Nutritional goals	18.047 (2.279, 142.922)	61.985 (2.496, 1539.326)	156.100 (8.497, 2867.799)	3.755 (0.332, 42.415)	0.484 (0.023, 10.047)	0.918 (0.044, 19.294)
2.165 (0.274, 17.088)	0.787 (0.218, 2.847)	0.123 (0.006, 2.464)	0.356 (0.019, 6.712)	1.009 (0.107, 9.537)	4.512 (0.473, 43.047)	1.974 (0.186, 20.958)	0.104 (0.011, 0.970)	1.802 (0.950, 3.417)	1.224 (0.210, 7.153)	3.000 (0.129, 69.777)	9.957 (1.223, 81.053)	0.055 (0.007, 0.439)	Placebo	3.435 (0.294, 40.073)	8.649 (1.069, 69.979)	0.208 (0.057, 0.758)	0.027 (0.003, 0.249)	0.051 (0.005, 0.475)
0.630 (0.025, 15.619)	0.229 (0.014, 3.668)	0.036 (0.001, 1.727)	0.104 (0.002, 4.768)	0.294 (0.011, 8.199)	1.314 (0.047, 36.896)	0.575 (0.019, 17.367)	0.030 (0.001, 0.839)	0.525 (0.041, 6.645)	0.357 (0.017, 7.343)	0.873 (0.016, 47.318)	2.899 (0.115, 73.288)	0.016 (0.001, 0.401)	0.291 (0.025, 3.397)	QoL	2.518 (0.100, 63.409)	0.061 (0.004, 0.973)	0.008 (0.000, 0.215)	0.015 (0.001, 0.410)
0.250 (0.014, 4.559)	0.091 (0.008, 1.033)	0.014 (0.000, 0.550)	0.041 (0.001, 1.513)	0.117 (0.005, 2.510)	0.522 (0.025, 10.979)	0.228 (0.010, 5.351)	0.012 (0.001, 0.257)	0.208 (0.026, 1.685)	0.142 (0.009, 2.184)	0.347 (0.008, 15.165)	1.151 (0.109, 12.212)	0.006 (0.000, 0.118)	0.116 (0.014, 0.935)	0.397 (0.016, 9.998)	Reduced incidence of late pneumonia	0.024 (0.002, 0.276)	0.003 (0.000, 0.065)	0.006 (0.000, 0.125)
10.403 (0.926, 116.816)	3.784 (0.875, 16.364)	0.592 (0.023, 15.467)	1.709 (0.069, 42.334)	4.849 (0.363, 64.754)	21.687 (1.724, 272.844)	9.486 (0.642, 140.190)	0.502 (0.038, 6.604)	8.659 (2.176, 34.463)	5.886 (0.660, 52.473)	14.418 (0.480, 432.854)	47.856 (4.148, 552.139)	0.266 (0.024, 3.008)	4.806 (1.319, 17.509)	16.507 (1.028, 265.072)	41.571 (3.622, 477.088)	Survival rate	0.129 (0.015, 1.114)	0.244 (0.018, 3.231)
0.737 (3.902, 1670.202)	29.362 (2.579, 334.287)	4.591 (0.110, 192.116)	13.261 (0.332, 529.535)	37.626 (1.590, 890.248)	168.292 (7.301, 3879.261)	73.611 (2.862, 1893.344)	3.897 (0.167, 91.049)	67.195 (6.766, 667.407)	45.673 (2.662, 783.523)	111.888 (2.368, 5286.967)	371.370 (17.570, 7848.675)	2.067 (0.100, 42.910)	37.297 (4.019, 346.125)	128.099 (4.647, 3530.871)	322.596 (15.328, 6789.958)	7.760 (0.898, 67.088)	Survival time	1.897 (0.081, 44.505)
42.555 (2.029, 892.476)	15.476 (1.176, 203.772)	2.420 (0.058, 101.657)	6.990 (0.174, 280.199)	19.832 (0.834, 471.397)	88.704 (3.708, 2122.182)	38.803 (1.502, 1002.448)	2.054 (0.198, 21.302)	35.421 (3.466, 361.948)	24.073 (2.348, 246.805)	58.980 (1.244, 2797.272)	195.742 (9.140, 4192.280)	1.089 (0.052, 22.895)	19.660 (2.105, 183.626)	67.518 (2.439, 1869.264)	170.051 (7.973, 3626.416)	4.091 (0.310, 54.055)	0.527 (0.022, 12.365)	Watery diarrhoea

Figure 2. A Prisma Flow Chart For Study Selection



on the identified effects of low caloric intake among critically ill patients. A box plot, a bubble plot, a summary of the meta-regression output, a forest plot of the mortality ranks of mortality data reported by the respective studies, and a funnel plot were generated to give an impression of the effects of the treatment. A meta-regression on LOS was performed using Microsoft Excel. Pearson correlation and the ANOVA test will be used to measure the correlation of two factors and the statistical significance, respectively. Regression analysis presented the LOS of the involved participants against the respective caloric quantities. The relationship coefficient of Pearson will be obtained to demonstrate the magnitude of the effects of low caloric intake. Additionally, $P < .05$ was considered as statistically significant. As for the confidence interval, the negative value represents the lower class, whereas the positive value represents the upper class. The 95% confidence interval will be used in the study.

RESULTS

Study Selection and Characteristics

The initial literature search generated 1357 publications in the electronic databases. A total of 22 studies (see Figure 2)(involving a total of 9 539 participants) were subjected to network meta-analysis. [4,16-34] The two independent reviewers agreed and settled on studies that met inclusion criteria, 97% through abstracts and 90% by titles. A total of 17 studies (77.27%) reported mortality rates, whereas 12 studies (54.55%) reported LOS outcomes. Lastly, three studies (13.64%) reported secondary outcomes. A total of 9 539 participants involved in the study were admitted to the ICUs, of which 2 678 (28.07%) were males.

Risk of Bias Assessment

According to Figures 3 and 4, green and red colour codes represented low and high risk of bias, respectively. The white area represented the unclear risk of bias.

Quality assessment outcomes of the individual studies are presented in Figure 3. The seven domains of quality

Figure 3. Risk Of Bias Graph: Review Authors' Judgements About Each Risk Of Bias Item

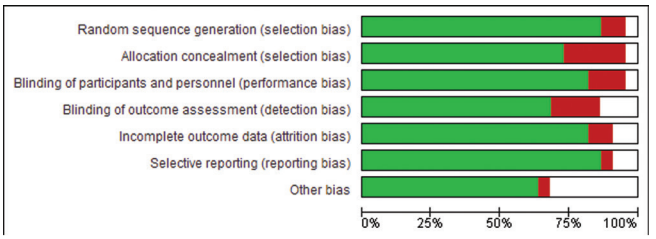
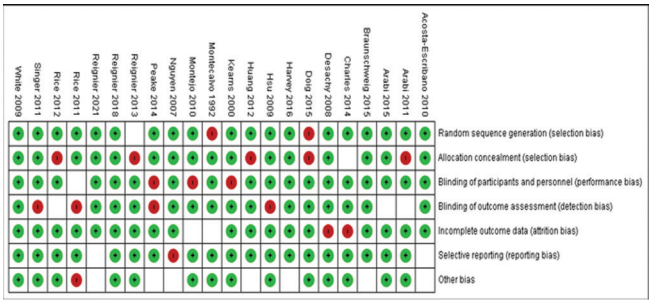


Figure 4. Risk Of Bias Summary: Review Authors' Judgements About Each Risk Of Bias Item



assessments are represented by the colour codes used in the risk assessment presented above.

Analysis of Primary Outcomes

Mortality Rates. We performed a meta-analysis on 17 studies reporting the mortality rates due to low-calorie intake among critically ill patients in the ICU. The meta-analysis was performed in three different phases. In the first phase, we ranked the average percentages of the resulting hospital mortality. Studies reporting hospital the rate of hospital mortality were ranked from the highest to the lowest (see Table 4).

According to Figure 5, the forest plot shows the weight of the treatment on the outcome. In this case, the long plot lines show the effect of the weight of low-calorie intake on the mortality rate of critically ill patients in ICUs. The mortality from four studies (Braunschweig et al.,[22] Singer et al.,[27] Huang et al.,[30] and Reignier et al.,[31]) ranked highest, whereas studies by Montecalvo et al.,[35] White et al.,[19] and Hsu et al.,[18] ranked lowest.

In the second phase, we created a corresponding bubble plot for the outcome (see Figure 6). A bubble plot of the average mortality percentages of the selected studies and their corresponding ranks was created. The bubble plot best explains the forest plots on the same. The bubble plot suggests the effect of low caloric intake in the intervention and control groups. The effect of low caloric intake is best explained through the corresponding mortality rates. Lastly, the third phase concerned statistical analysis based on mortality rates and ranks to investigate potential trends and patterns.

According to Figure 7, we found an increased mortality rate with an increase in the consumption of calories among critically ill patients. The box plot below presents the overall mortality pattern in the intervention group. Mortality rates are seemingly

Table 4. Ranks Of The Average Percentage Of The Mortality Rates

study	95% CI		Average	Rank
	IG	CG		
Arabi et al., 2011	18	23	20.5	8
Rice et al., 2011	22.4	19.6	21	7
Rice et al., 2012	23.2	22.2	22.7	6
Charles et al., 2014	7.3	9.5	8.4	11
Montecalvo et al., 1992	11.2	15.9	13.55	8
Kearns et al., 2000	35	34	34.5	3
Nguyen et al., 2007	13	17	15	6
Desachy et al., 2008	11	11	11	6
Hsu et al., 2009	7	7.2	7.1	7
White et al., 2009	3	5	4	8
Montejo et al., 2010	17	21	19	5
Acosta-Escribano et al., 2010	8	10	9	5
Singer et al., 2011	32.3	47.7	40	1
Huang et al., 2012	30	49.3	39.65	1
Reignier et al., 2013	6.7	7.1	6.9	3
Peake et al., 2014	20	37	28.5	1
Braunschweig et al., 2015	40	16	28	1

Figure 5. A Forest Plot of The Ranks of The Mortality Rates.

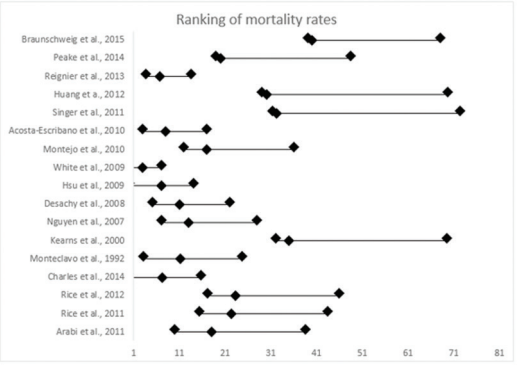


Figure 6. A Bubble Plot For The Mortality Rates

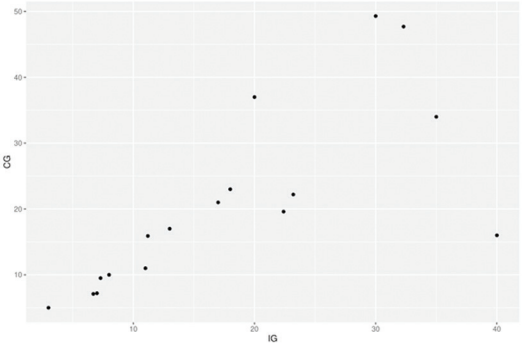


Figure 7. A Box Plot Of The Mortality Rates In The High And Low Caloric Group

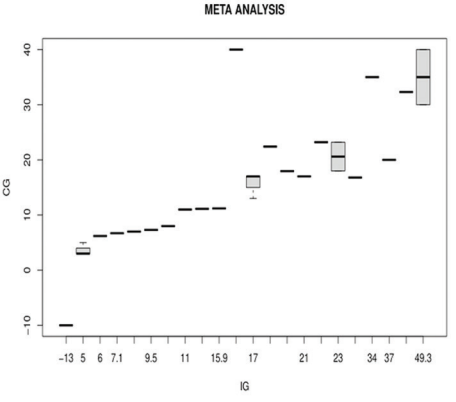


Table 5. A Summary Of Low Differences In The Mortality Rates.

	Low caloric intake (%)	High caloric intake (%)	% Difference
Kearns et al., 2000	35	34	1
Desachy et al., 2008	11	11	0
Hsu et al., 2009	7	7.2	-0.2
Acosta-Escribano et al., 2010	8	10	-2

Figure 8. A bubble plot for LOS as an effect low calorie

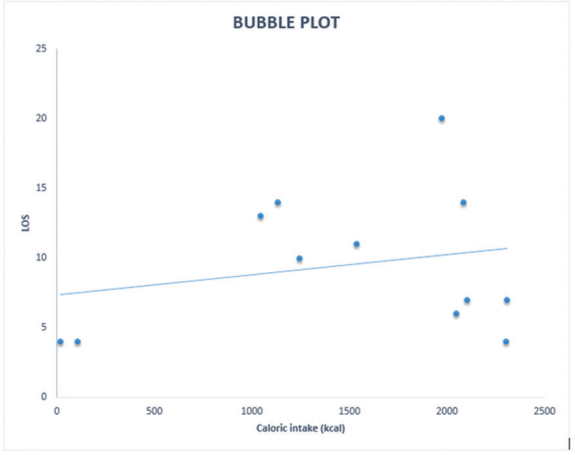


Table 6. Linear Regression Of Los Effects Of Low Caloric Intake

Summary Output								
Regression Statistics								
Multiple R	0.230020383							
R Square	0.052909376							
Adjusted R Square	-0. 041799686							
Standard Error	818.088245							
Observations	12							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	1	373887.9004	373887.9	0.558652	0.472013641			
Residual	10	6692683.766	669268.4					
Total	11	7066571.667						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1144. 303084	520.3116554	2.199265	0.052506	-15.02353039	2303.629699	-15.02353039	2303.629699
X Variable 1	36. 47686833	48. 80305313	0. 74743	0.472014	-72.26311045	145.2168471	-72.26311045	145.2168471

Table 7. Secondary Outcomes Reported By The Meta-Analyzed Studies

Variable	Number of Studies	Rank
Nosocomial infections	19	1
Clinical outcomes	21	1
Functions	19	2
Digestive infections	1	4
Improved Quality of life	20	2
Survival rate	18	5
Ventilator days	3	6
Bacteremia	7	6
Blood glucose levels	8	6
Diarrhea	13	6
Tube replacement	3	9

increasing in the intervention group with increased caloric intake. The low caloric intake resulted in low mortality rates.

Studies by Kearns et al,[25] Desachy et al.,[17] Hsu et al.,[18] Acosta-Escribano et al.,[26] and Reignier et al.,[31] reported relatively lower mortality rates between the treatment and the control group. Table 5 shows the percentage differences between the mortality rates of the low and high-caloric intake groups, which show positive and negative differences. Studies by Kearns et al.[25] and Desachy et al.[17] reported higher mortality rates in the low-caloric intake group than in the high-intake group. Nonetheless, the difference was small between the two groups.

LOS

We performed a meta-analysis on 12 studies to determine the effect of adopted low calories on patients' vital signs in the nutritional support of critically ill in ICUs. First, we measured the effect of the low caloric intake vs. the number of hospital stays (LOS). We plotted a bobble plot to measure the relationship and magnitude of the effect, length of hospital stay, and intervention (see Figure 8).

According to Figure 8, the meta-regression and the correlation between caloric intake and LOS could not explain the length of hospital stay, which is justified by the high standard error established in the meta-regression. The outcome was not statistically significant (P = .47). We found that the 12 studies displayed a weak positive correlation between low caloric intake and LOS. Since the caloric intake in the 12 studies cannot explain the length of hospital stay reported, the weak positive correlation between the two aspects can be justified.

Table 6 presents the summary output of the meta-regression of the correlation between caloric intake and the number of hospital stays, where we found a significant standard error, 818.09 out of the 12 observations. A high heterogeneity could have been responsible for this variability. The linear regression used 12 studies reporting LOS as an adequate low-caloric intake. The analysis of the 12 observations was not statistically significant (F (1, 10) = 0.55, 95% CI [-72.26 to 145.22], P = .47). Also, we found a positive correlation between low caloric intake and LOS (r = 0.23).

Analysis of Secondary Outcomes

We found secondary effects of low caloric intake among patients with vital signs in the nutritional support for critically ill patients in ICUs. Table 7 summarises the secondary outcomes reported by the included studies: nosocomial infection, clinical outcomes, functions, digestive infections, improved quality of life, resulting survival rates, ventilator days, bacteremia, blood glucose levels, diarrhoea, and tube replacement. We ranked the number of studies reporting a particular outcome. Nosocomial infections and clinical outcomes ranked the highest, whereas survival rate and ventilator days ranked lowest.

DISCUSSION

Our study established that the length of hospital stay as an effect of adopting low caloric intake established a weak positive correlation. This finding is of great clinical significance. The observation from the 12 studies indicates that low caloric intake can potentially increase the length of hospital stay among critically ill patients in ICUs.

Our findings corroborate the outcomes of a previously performed meta-analysis, where it was reported that critically ill patients might tolerate long spells of underfeeding alongside the reduction of side effects like reduced lengths of

hospital stay.[36] However, our meta-analysis contraindicates the generalisation of the study findings by indicating that these outcomes are patient-specific and dynamic among patients. These findings could explain the high standard error and the clinically insignificant outcomes reported in the present study.

Although the 14 studies had a high heterogeneity, the difference in caloric intake was relatively small because of the high variance in the number of participants. Nevertheless, this is another explanation for the weak positive correlation between LOS and the effect of adopting low caloric intake. The present study's findings corroborate Siqueira-Paese et al.,[37] who showed that low caloric intake reduces LOS. The effect of adopting a low-caloric diet remains unclear and controversial.[38] Nonetheless, it is of great clinical significance since nutrition is considered a crucial therapeutic phenomenon among critically ill patients.[1,2]

We found a weak positive correlation between LOS and low caloric intake among critically ill patients in ICUs. The ANOVA test confirmed that low caloric intake potentially decreases LOS among the critically ill in ICUs. We measured the size of the difference in the effect of low caloric intake based on the data provided by the included studies. We found a statistically acceptable outcome that suggests the evidence from the included studies is strong.[39] Despite the statistically acceptable outcomes, further studies should be conducted as the outcomes of this study might not reflect the actual aspect of critical illnesses and enteral feeding.

A visual inspection of the bubble plot showed a linear relationship between LOS and caloric intake, where higher caloric intake translated to prolonged LOS, and the converse is true. Similarly, Howell et al.[40] established a direct relationship between LOS and the quantities of calories consumed. Our study found that adopting low caloric consumption implicates mortality among critically ill patients in ICUs. The bubble plots revealed a clear impression of the nutritional outcomes of low-calorie intake, with the dots concentrated in a pattern, suggesting a linear relationship between the intervention group and the control.

Our findings showed decreased mortality rates among critically ill patients following the intervention by low-calorie intakes. We propose that mortality rates increase with caloric consumption. Clinically, critically ill patients in ICUs should consume low-calorie foods. The present study corroborates the outcomes from two studies (Siqueria-Paese et al.,[37] Parikh et al.,[41]). Siqueira-Paese et al.[37] found that low-caloric foods decreased mortality among critically ill patients in ICUs. In contrast, Parikh et al.[41] reported a 26% decrease in mortality among low-calorie delivery participants. We could deduce that the mortality rates of the critically ill increased with increased caloric consumption.

Our study found that increased calorie intake increases the mortality rates in the intervention group. A hypothetical trend line of best fit produced a linear relationship between the mortality rates in the intervention group. Five studies (Kearns et al.,[25] Desachy et al.,[17] Hsu et al.,[18] Acosta-Escribano et al.,[26] Reignier et al.,[32]) reported minimal differences in the mortality rates in the low-caloric and high-caloric delivery groups. Although decreased rates of mortality rate were observed in the low-caloric group, we found that low caloric intake does not significantly decrease mortality rates. We found a positive and negative difference in the percentages of mortality rates in the low and high-caloric groups. These outcomes were consistent with Chelkeba et al.[42]

Chelkeba et al.[42] compared the mortality between high and low caloric intake and found that the difference was insignificant. However, the drawback with this comparison regards the varying caloric quantities used by Chelkeba et al. Similarly, in our study, we could not work with a standard caloric quantity since the studies were performed using different caloric quantities. High variation in caloric quantities is a risk factor for bias. Future studies should include studies with relatively equal caloric quantities for proper network meta-analysis.

Limitations and Areas of Further Research

A notable limitation of the present study is the inclusion of studies with small participant groups, with some studies having participant numbers well below 100, such as those by Nguyen et al.,[16] Charles et al.,[21] Braunschweig et al.,[22] Kearns et al.,[25] Montecalvo et al.,[35] and Reignier et al.[31] These small sample sizes do not represent the broader critically ill patient population, leading to under-representation. Caution is advised when interpreting the outcomes, and future network meta-analyses should prioritise studies with more significant participant numbers to ensure more accurate representation.

Additionally, while our study found that adopting low caloric intake improved the quality of life and reduced morbidity among critically ill patients in ICUs, it also revealed secondary outcomes, including nosocomial infection, clinical outcomes, functions, digestive infections, improved quality of life, survival rates, ventilator days, bacteremia, blood glucose levels, diarrhoea, and tube replacement. However, the lack of specification regarding the particular disease status of critically ill patients is a limitation. Future investigations could address this by establishing a standard caloric intake measure across all critical illnesses or focusing on specific illnesses to provide more precise and meaningful conclusions.

Furthermore, some included studies reported minimal differences in mortality rates between intervention and control groups, necessitating further investigation into the underlying reasons. The high variability in outcomes reported by the included studies, particularly regarding the length of hospital stay, poses challenges in interpretation, likely stemming from significant heterogeneity among the studies due to differences in patient illness severity and disease types. This underscores the need for caution when generalising the findings.

Future research should prioritise standardisation in defining low-caloric intake, consider larger-scale studies, and explore subgroups of critically ill patients with specific conditions or diagnoses to provide more targeted insights.

Additionally, investigating the long-term effects of low-caloric intake on patient outcomes is a worthwhile avenue for further exploration.

CONCLUSION

Our study represents a significant advancement in the field while acknowledging the existing research on the nutritional support of critically ill patients in ICUs. Notably, this research is the first network meta-analysis conducted in this area, allowing for a comprehensive evaluation of low-caloric intake strategies among critically ill patients. This innovative methodological approach enables us to synthesise and compare data from multiple direct and indirect studies to provide a more comprehensive and nuanced understanding of the effects of low-caloric intake. By adopting this approach, our study aims to offer a more robust and evidence-based perspective on the impact of low-caloric intake on mortality rates, length of stay, and quality of life, ultimately contributing to improved clinical decision-making and patient care strategies. While building upon previous research, this study's unique methodology enhances its value and relevance within the scientific community and clinical practice.

Practically, our findings carry significant implications for healthcare professionals and policymakers alike. The evidence we present can guide healthcare practitioners in optimising nutritional strategies for critically ill patients in ICUs. Specifically, our study suggests that low-caloric intake may lead to reduced mortality rates and shorter lengths of stay without compromising the quality of life. These findings imply that individualised nutritional plans, considering low-caloric intake when appropriate, may benefit critically ill patients' care. Healthcare professionals can use this information to tailor nutritional support more precisely, potentially reducing complications and improving overall outcomes. Moreover, policymakers responsible for shaping healthcare guidelines and policies can consider our study's insights when formulating recommendations for nutritional support in ICUs. Evidence-based practices should integrate the findings of this research into guidelines for addressing critically ill patients' nutritional needs, potentially leading to improved patient care and resource allocation.

However, it is essential to acknowledge the presence of heterogeneity among some analyses, which may be attributed to variations in study methodologies, patient populations, and nutritional protocols.[43-47] This variability, while challenging, also reflects the real-world complexity of ICU care. Therefore, while our findings provide valuable insights, their generalizability should be considered within the context of this heterogeneity. Our findings suggest that, when appropriately applied, low-caloric intake strategies may reduce mortality rates and length of stay without compromising quality of life.

REFERENCES

1. Mehta Y, Sunavala JD, Zirpe K, et al. Practice guidelines for nutrition in critically ill patients: a relook for Indian scenario. *Indian J Crit Care Med*. 2018;22(4):263-273. doi:10.4103/ijccm.IJCCM_3_18
2. Yatabe T. Strategies for optimal calorie administration in critically ill patients. *J Intensive Care*. 2019;7(1):15. doi:10.1186/s40560-019-0371-7
3. Harvey SE, Parrott F, Harrison DA, et al. A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). *Health Technol Assess*. 2016;20(28):1-144. doi:10.3310/hta20280
4. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27(5):355-373. doi:10.1177/0148607103027005355
5. Secombe P, Harley S, Chapman M, Aromataris E. Feeding the critically ill obese patient: a systematic review protocol. *JBI Database Syst Rev Implement Reports*. 2015;13(10):95-109. doi:10.11124/jbisrir-2015-2458
6. Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE. LEEP-COVID Study Group John Whittle Jeroen Molinger David MacLeod Krista Haines Paul E. Wischmeyer Anthony Sung Marat Fudim Lindsie Boerger Kathryn Lessig Jessica Lumbard Leslie C. Murray Sue Steves Jhana Parikh Jacob Ribet Melanie Hollidge. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. *Crit Care (Fullerton)*. 2020;24:1-4.
7. Indrio F, Neu J, Pettoello-Mantovani M, et al. Development of the gastrointestinal tract in newborns as a challenge for an appropriate nutrition: A narrative review. *Nutrients*. 2022;14(7):1405. doi:10.3390/nu14071405
8. Bering J, DiBaise JK. Home parenteral and enteral nutrition. *Nutrients*. 2022;14(13):2558. doi:10.3390/nu14132558
9. Prest PJ, Justice J, Bell N, McCarroll R, Watson CM. A volume-based feeding protocol improves nutrient delivery and glycemic control in a surgical trauma intensive care unit. *JPEN J Parenter Enteral Nutr*. 2020;44(5):880-888. doi:10.1002/jpen.1712
10. Hoffmann M, Schwarz CM, Fürst S, et al. Risks in management of enteral nutrition in intensive care units: a literature review and narrative synthesis. *Nutrients*. 2020;13(1):82. doi:10.3390/nu13010082
11. Ojo O, Keaveney E, Wang XH, Feng P. The effect of enteral tube feeding on patients' health-related quality of life: a systematic review. *Nutrients*. 2019;11(5):1046. doi:10.3390/nu11051046
12. Larsen JA. Enteral nutrition and tube feeding. Applied veterinary clinical nutrition. 2023 Aug 23:515-45. doi:10.1002/9781119375241.ch20
13. Lappas BM, Patel D, Kumpf V, Adams DW, Seidner DL. Parenteral nutrition: indications, access, and complications. *Gastroenterol Clin North Am*. 2018;47(1):39-59. doi:10.1016/j.gtc.2017.10.001
14. Moher D, Shamseer L, Clarke M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1-9. doi:10.1186/2046-4053-4-1
15. Shamseer L, Moher D, Clarke M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350(jan02 1):g7647. doi:10.1136/bmj.g7647
16. Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: one drug or two? *Crit Care Med*. 2007;35(11):2561-2567. doi:10.1097/01.CCM.0000286397.04815.B1
17. Desachy A, Clavel M, Vuagnat A, Normand S, Gissot V, François B. Initial efficacy and tolerability of early enteral nutrition with immediate or gradual introduction in intubated patients. *Intensive Care Med*. 2008;34(6):1054-1059. doi:10.1007/s00134-007-0983-6
18. Hsu C-W, Sun S-F, Lin S-L, et al. Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. *Crit Care Med*. 2009;37(6):1866-1872. doi:10.1097/CCM.0b013e31819ffcda
19. White H, Sosnowski K, Tran K, Reeves A, Jones M. A randomised controlled comparison of early post-pyloric versus early gastric feeding to meet nutritional targets in ventilated intensive care patients. *Crit Care*. 2009;13(6):R187. doi:10.1186/cc8181
20. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr*. 2011;93(3):569-577. doi:10.3945/ajcn.110.005074
21. Charles EJ, Petroze RT, Metzger R, et al. Hypocaloric compared with eucaloric nutritional support and its effect on infection rates in a surgical intensive care unit: a randomized controlled trial. *Am J Clin Nutr*. 2014;100(5):1337-1343. doi:10.3945/ajcn.114.088609
22. Braunschweig CA, Sheean PM, Peterson SJ, et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT). *JPEN J Parenter Enteral Nutr*. 2015;39(1):13-20. doi:10.1177/0148607114528541
23. Arabi YM, Aldawood AS, Haddad SH, et al; PermiT Trial Group. Permissive underfeeding or standard enteral feeding in critically ill adults. *N Engl J Med*. 2015;372(25):2398-2408. doi:10.1056/NEJMoa1502826
24. Doig GS, Simpson F, Heighes PT, et al; Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. *Lancet Respir Med*. 2015;3(12):943-952. doi:10.1016/S2213-2600(15)00418-X
25. Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. *Crit Care Med*. 2000;28(6):1742-1746. doi:10.1097/00003246-200006000-00007
26. Acosta-Escribano J, Fernández-Vivas M, Grau Carmona T, et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. *Intensive Care Med*. 2010;36(9):1532-1539. doi:10.1007/s00134-010-1908-3
27. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*. 2011;37(4):601-609. doi:10.1007/s00134-011-2146-z
28. Rice TW, Wheeler AP, Thompson BT, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomised trial. *JAMA*. 2012;307(8):795-803. doi:10.1001/jama.2012.137
29. Montejo JC, Miñambres E, Bordejé L, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med*. 2010;36(8):1386-1393. doi:10.1007/s00134-010-1856-y
30. Huang H-H, Chang S-J, Hsu C-W, Chang T-M, Kang S-P, Liu M-Y. Severity of illness influences the efficacy of enteral feeding route on clinical outcomes in patients with critical illness. *J Acad Nutr Diet*. 2012;112(8):1138-1146. doi:10.1016/j.jand.2012.04.013
31. Reignier J, Le Gouge A, Lascarrou J-B, et al. Impact of early low-calorie low-protein versus standard-calorie standard-protein feeding on outcomes of ventilated adults with shock: design and conduct of a randomised, controlled, multicentre, open-label, parallel-group trial (NUTRIREA-3). *BMJ Open*. 2021;11(5):e045041. doi:10.1136/bmjopen-2020-045041
32. Reignier J, Mercier E, Le Gouge A, et al; Clinical Research in Intensive Care and Sepsis (CRICS) Group. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. *JAMA*. 2013;309(3):249-256. doi:10.1001/jama.2012.196377
33. Reignier J, Boisramé-Helms J, Brisard L, et al; NUTRIREA-2 Trial Investigators; Clinical

Research in Intensive Care and Sepsis (CRICS) group. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). *Lancet*. 2018;391(10116):133-143. doi:10.1016/S0140-6736(17)32146-3
34. Peake SL, Davies AR, Deane AM, et al; TARGET investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial. *Am J Clin Nutr*. 2014;100(2):616-625. doi:10.3945/ajcn.114.086322
35. Montecalvo MA,et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. *Crit Care Med*. 1992 Oct;20(10):1377-87.
36. Tatucu-Babet OA, Ridley EJ. How much underfeeding can the critically ill adult patient tolerate? *J Intensive Med*. 2022;2(2):69-77. doi:10.1016/j.jointm.2022.01.002
37. Siqueira-Paese MC, Dock-Nascimento DB, De Aguilar-Nascimento JE. Critical energy deficit and mortality in critically ill patients. *Nutr Hosp*. 2016;33(3):253.
38. Al-Dorzi HM, Albarrak A, Ferwana M, Murad MH, Arabi YM. Lower versus higher dose of enteral caloric intake in adult critically ill patients: a systematic review and meta-analysis. *Crit Care*. 2016;20(1):358. doi:10.1186/s13054-016-1539-3
39. Dahiru T. P - value, a true test of statistical significance? A cautionary note. *Ann Ib Postgrad Med*. 2008;6(1):21-26.
40. Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. *Am J Physiol Endocrinol Metab*. 2017;313(5):E608-E612. doi:10.1152/ajpendo.00156.2017
41. Parikh HG, Miller A, Chapman M, Moran JL, Peake SL. Calorie delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis. *Crit Care Resusc*. 2016;18(1):17-24.
42. Chelkeba L, Mojtahedzadeh M, Mekonnen Z. Effect of calories delivered on clinical outcomes in critically ill patients: systemic review and meta-analysis. *Indian J Crit Care Med*. 2017;21(6):376-390. doi:10.4103/ijccm.IJCCM_453_16
43. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Stat Med*. 1998;17(8):841-856. doi:10.1002/(SICI)1097-0258(19980430)17:8<841::AID-SIM781>3.0.CO;2-D
44. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557
45. Petitti DB. Approaches to heterogeneity in meta-analysis. *Stat Med*. 2001;20(23):3625-3633. doi:10.1002/sim.1091
46. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. *Crit Care Med*. 2011;39(5):967-974. doi:10.1097/CCM.0b013e31820a905a
47. Mehta Y, Mithal A, Kulkarni A, et al. Practice guidelines for enteral nutrition management in dysglycemic critically ill patients: a relook for Indian scenario. *Indian J Crit Care Med*. 2019;23(12):594-603. doi:10.5005/jp-journals-10071-23298