Original Article

Initial energy supplementation in critically ill patients receiving enteral nutrition: a systematic review and meta-analysis of randomized controlled trials

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Background and Objectives: Here we systematically reviewed and quantitatively analyzed randomized controlled trials (RCTs) to compare the important initial outcomes of critically ill adults receiving low- and high-energy enteral nutrition. **Methods and Study Design:** RCTs comparing low- and high-energy supplementation in critically ill adults receiving enteral nutrition admitted to the intensive care unit for an expected stay of >48 h were included. Abstracts submitted to major scientific meetings were included and the primary endpoint was mortality. The risk ratio (RR) and weighted mean difference (WMD) with 95% confidence intervals (CIs) were the effect measures. **Results:** Eleven RCTs (3,212 patients) were included. The groups did not differ significantly in mortality (RR, 0.94; 95% CI, 0.80-1.11; p=0.47), infections morbidity (RR 1.09; 95% CI 0.95-1.26; p=0.23), pneumonia morbidity (RR 1.04; 95% CI 0.88-1.23; p=0.68), hospital length of stay (WMD -0.27; 95% CI -3.21 to 3.76; p=0.88), intensive care unit length of stay (WMD -0.32; 95% CI, -1.81 to 1.16; p=0.46), mechanical ventilation days (WMD -0.30; 95% CI-1.42 to 0.82; p=0.60). The incidence of gastrointestinal intolerance was significantly lower in the low-energy group (RR 0.79; 95% CI 0.65-0.97; p<0.05). **Conclusions:** The initial administration of low- versus high-energy supplements did not impact clinical outcomes except for gastrointestinal intolerance in non-malnourished critically ill patients receiving enteral nutrition. The initial administration of high- rather than low-energy may benefit these patients by reducing infections, but this effect might actually be attributable to the concomitant high protein intake.

Key Words: critical illness, enteral nutrition, meta-analysis, energy intake, protein intake

INTRODUCTION

Critically ill patients are at increased risk of developing progressive malnutrition due to insufficient enteral intake and sustained hypercatabolism.[1] Nutrition support methods including enteral nutrition (EN) and parenteral nutrition (PN) are used to meet the energy demands and optimize the clinical outcomes of patients in the intensive care unit.[2-4] Previous reports established that EN improves outcomes during critical illnesses and is the optimal route of nutrition in patients with adequate gastrointestinal tract function.[2,5,6]

EN supports intestinal structure and function since it promotes the normal synthesis and release of antimicrobial peptides associated with mucosal immunity, protects epithelial cells, improves tight junctions, and ultimately prevents intestinal barrier function breakdown and subsequent bacterial translocation.[7-9] Furthermore, a recent meta-analysis found that successful EN initiation in critically ill patients was associated with significantly reduced mortality rates.[10] Accordingly, the guidelines of both the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism advocate early EN use for patients with critical illnesses;[2,3] however, this can induce gastrointestinal intolerance, which subsequently leads to a decreased caloric intake.[11-13] Supplemental PN (SPN) can be used to help achieve target caloric goals, but whether it can provide benefits has not been established. In other words, whether the use of SPN is necessary to meet the patients' target energy needs during the early days of treatment once target energy needs cannot be supplied by EN remains to be elucidated.

The precise correlation between caloric intake levels and patient outcomes is currently unclear. Clinical cohort studies have demonstrated that a continuous low-energy (LE) intake is harmful for patients,[14-16] and the updated Canadian critical care nutrition guidelines still recommend achieving the target energy intake.[17] However, oth-

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ers have shown that an initial lower caloric intake in critically ill patients is not associated with significantly worse outcomes.[18-21] Permissive underfeeding and trophic feeding is the administration of small volumes of enteral solution; this process allows the gastrointestinal tract to adjust to feeding. This was originally used to improve outcomes for low birth weight infants[22] and the clinical benefits of initial lower energy feeding in critically ill adult patients have not yet been determined.

The purpose of this study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the impact of initial different energy nutrition support on relevant clinical outcomes in critically ill patients receiving EN.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy

We conducted a systematic review of the published literature to identify all relevant clinical trials using keywords or Medical Subject Headings of enteral nutrition, parenteral nutrition, critical illness, critically ill, ICU, early, and initial, in combination with the Boolean operators AND and OR. To identify these articles, two authors independently performed computerized searches on MEDLINE, EMBASE, and the Cochrane Controlled Trials Register Database. We also searched comprehensive review articles for additional primary studies. The final closeout date for the search process was May 1, 2015. No language restrictions were placed on the searches. Additionally, abstracts submitted to major scientific meetings were deemed acceptable if a copy of the manuscript was available to complete data extraction. Authors were approached for additional or missing data if necessary.

Inclusion criteria

Two investigators independently retrieved and reviewed all original studies, which were selected for inclusion if they met the following criteria:

1. Research design: randomized clinical trial
2. Population: critically ill adults admitted to the intensive care unit (ICU) and expected to stay for more than 48 h
3. Intervention: significantly different calorie intakes in two groups
4. Follow-up: patients in the two groups received isocaloric nutrition when the period of study was over
5. Clinical outcome: overall patient mortality

Exclusion criteria

Studies were excluded if they met the following criteria:

1. Study population included critically ill infants or children (<10 years of age)
2. EN was given for less than 3 days
3. Calorie intake of patients in low energy group was more than 80% of target energy

Data extraction

Two authors independently performed data abstraction which included sample size, demographics, illness severity, nutrition duration and regimen, mean daily percentage of the caloric goal and protein intake, clinical outcome, and risk of bias.

Assessment of risk of bias

Two investigators independently assessed the risk of bias in each study using the methods detailed in the Cochrane Handbook for Systematic Reviews of Interventions.[23] Disagreements were resolved by investigator consensus.

Analysis

The primary outcome of this systematic review was overall mortality. We combined hospital mortality of all studies reported; if hospital mortality was not reported, we used 60- or 90-day mortality. Secondary outcomes included infections (bacteremia or sepsis if infection was not reported), pneumonia (including ventilator-associated and infectious pneumonia); hospital and ICU length of stay (LOS-HOS and LOS-ICU, respectively); and mechanical ventilation days (MVD). Gastrointestinal intolerance involves symptoms of gastrointestinal dysfunction such as vomiting, noninfectious diarrhea and abdominal distension.

The common risk ratio (RR) and associated 95% confidence intervals (CIs) for death and risk of new infections and pneumonia were estimated. We estimated the overall weighted mean difference (WMD) with 95% CIs for LOS and MVD. The more conservative random effects model was used in this meta-analysis due to anticipated heterogeneity. Statistical heterogeneity was expressed as the I^2 statistic in which a result of more than 50% indicates significant heterogeneity. We planned subgroup analyses to determine the source of heterogeneity. Funnel plots were used to assess possible bias in reporting and publication, and pooled data are presented as Forest plots with Review Manager (RevMan), version 5.2 (used for all statistical analyses).

RESULTS

Description of eligible studies

The detailed search strategy is illustrated in the flow diagram in Figure 1, recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses group. Eleven RCTs[24-34] published between 1999 and 2015 fulfilled the inclusion criteria. A total of 3,212 patients without prior malnutrition were included in this meta-analysis, with 1,610 and 1,602 patients assigned to the low-energy (LE) and high-energy (HE) feeding groups, respectively. Among the eligible eleven studies, one was performed at the medical and surgical ICUs within the same hospital.[26]

Risk of bias in included studies

Randomization methods were reported in all included studies which were through number table randomizations or were computer generated.[24-34] Allocation concealment using a sealed envelope was documented in nine searches,[24-32] and although one study did not state allocation concealment; we agreed that there was a low risk of bias given their allocation method of web-based randomization.[33] As the different nutrition dosage and the need for

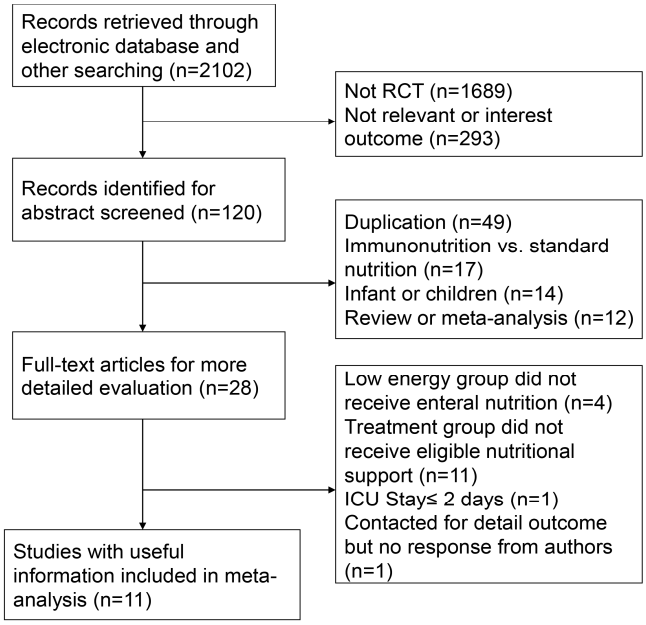

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and accompanying study flow diagram

titration was based on gastrointestinal tract function, only three studies reported blinding of participants, treatment providers, and investigators.[26,31,34] Investigator blinding was reported in another study.[30] Protocol violation after randomization occurred in six studies,[24,25,28,30,31,33] and intention-to-treat analysis was reported in eight studies.[24-26,28,30-33] A summary of the risk of bias in the included studies and each risk of bias factor are presented as percentages across all included studies in Figure 2. If more than four studies were included, funnel plots were used to assess possible reporting or publication bias. The funnel plots on mortality, infections and LOS-HOS are roughly symmetrical respectively. But the funnel plot on LOS-ICU shows publication bias; in light of this, we performed a sensitivity analysis to evaluate the robustness of the pooled outcome. When statistical heterogeneity was analyzed by subgroup analysis or sensitivity analysis, the funnel plots on mortality, infectious complications, pneumonia morbidity, and LOS-HOS were approximately symmetrical.

Characteristics of included studies

The basic characteristics of patients in the included studies are provided in Tables 1 and 2. All eligible patients could receive EN and their mean age was >50 years in ten studies, the mean age was <35 years old in one study.[34] The intervention duration in four of the studies was seven days;[24,26,32,34] one was six days;[33] two were five days (from the fourth to eighth day in one study);[29,30] and four studies were for more than 10 days.[25,27,28,31] Nine studies described the Acute Physiology And Chronic Health Evaluation II (APACHE II) score,[24-28,30-32,34] one stated the APACHE III score[33] and another one used the Simplified Acute Physiology Score;[29] only two study reported a score <20.[28,34] Patients of two groups in nine of the studies received EN only,[24,25,27-29,31-34] but patients in the high energy group in another two studies received both EN and PN.[26,30] The mean daily percentage of the caloric goal differed between groups. Patients in one research group received a similar dose of EN and a significantly different dose of PN in the LE and HE groups; however, we were only able to obtain the median daily percentage of the caloric goal.[34] Seven of the eleven studies showed the mean daily protein intake;[24,25,27,28,30-32] however, another

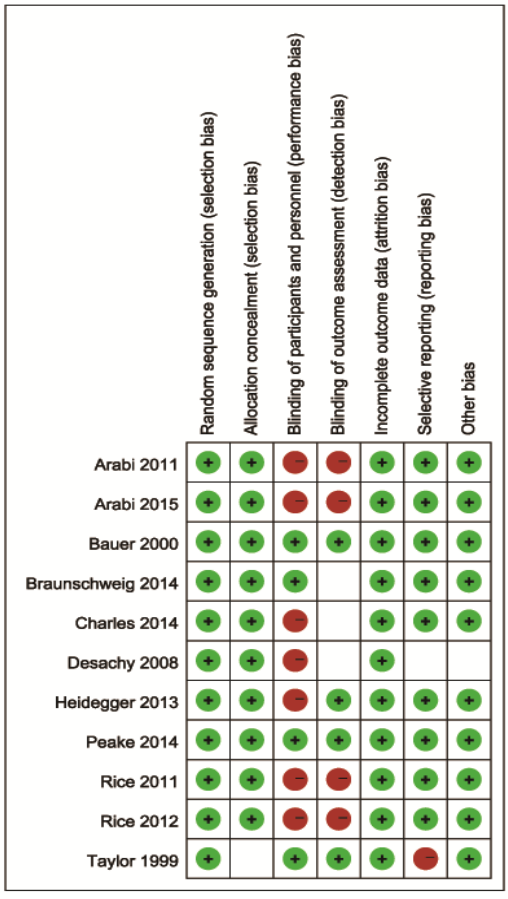

Figure 2. Risk of bias summary: authors' judgments regarding each risk of bias factor for included studies

Table 1. Characteristics of the enrolled studies

Study	NO. randomized		Characteristics of patients	Mean age (SD)		Duration of intervention
	LE	HE		LE	HE	
Arabi et al	120	120	>18 years old ICU >48 hours	50.3 (21.3)	51.9 (22.1)	1-7 day
Arabi et al	447	445	>18 years old ICU >72 hours EN within 48 hours of ICU admission	50.2 (19.5)	50.9 (19.4)	14 day
Bauer et al	60	60	>18 years old ICU >48 hours	55 (18)	53 (18)	1-7 day
Braunschweig et al	38	40	medical or surgical ICU >18 years old Within 24 hours of ALI	58.6 (16.2)	52.5 (17.1)	1-20 day
Charles et al	41	42	>18 years old Artificial Nutrition >48 h ICU >48 hours	50.4 (17.9)	53.4 (17.5)	10-12 day
Desachy et al	50	50	Medical or surgical ICU >18 years old	64 (13)	58 (19)	1-5 day
Heidegger et al	153	152	ICU>5 day Survive>7 day	60 (16)	61 (16)	4-8 day
Peake et al	55	57	>18 years old Enteral nutrition ≥ 2 days Mechanical ventilation	56.5 (16.1)	56.4 (16.8)	10 day
Rice et al	98	102	ICU admission Mechanical ventilation > 72 hours	53 (19)	54 (17)	0-6 day
Rice et al	508	492	ICU admission ALI <48 hours Mechanical ventilation >72 hours	52 (17)	52 (6)	1-6 day
Taylor et al	41	41	Patients of head injury necessitating mechanical ventilation Glasgow Coma Scale >3 >10 years old	28	34	1-7 day

LE: low energy; HE: high energy; ICU: intensive care unit; ALI: acute lung injury; SD: standard deviation.

Table 2. Characteristics of the enrolled studies continued

Mean of APACHE Ⅱ/Ⅲ score (SD)		Regimen of nutrition		Mean daily percentage of caloric goal (%)		Mean daily protein intake (g)	
LE	HE	LE	HE	LE	HE	LE	HE
25.2 (7.5)	25.3 (8.2)	EN	EN	59.0	71.4	47.5	43.6
21.0 (7.9)	21.0 (8.2)	EN	EN	46	71	57	60
N/A	N/A	EN	EN+PN	46.4	90.9	N/A	N/A
27.7 (7.9)	23.4 (9.3)	EN	EN	55.4	84.7	60.4	82
16.6(0.9)	17.3 (0.8)	EN	EN	40.5	73	86	83
40 (11)‡	42 (17)‡	EN	EN	76	95	N/A	N/A
23 (7)	22 (7)	EN	EN+PN	77	103	61.8	89.8
22 (8.9)	23 (9.1)	EN	EN	72	102	70	74
26.9 (8.1)	26.9 (6.6)	EN	EN	15	74.8	10.9	54.4
92 (28)†	90 (27)†	EN	EN	25	80	N/A	N/A
14	14	EN	EN	36.8	59.2	37.9%§	68.7%§

LE: low energy; HE: high energy; ICU: intensive care unit; ALI: acute lung injury; SD: standard deviation.
‡Mean of SAPS Ⅱ, SAPS Ⅱ: Simplified Acute Physiology Score Ⅱ.
†Mean of APACHE Ⅲ score, APACHE Ⅱ/Ⅲ: Acute Physiology and Chronic Health Evaluation Ⅱ/Ⅲ.
§The protein intake was replaced by the percentage of protein requirement as it was not available.

described the mean daily percentage of protein intake only[34] (Tables 1-2).

Meta-analysis of primary outcome

On the basis of meta-analysis of the eleven studies and subgroup analysis performed according to different strategies of nutrition support, mortality was not significantly different for patients initially receiving LE compared with HE (RR 0.94; 95% CI 0.80-1.11; p=0.47). The test for heterogeneity also revealed no significant differences (I^2=23%; p=0.22) (Figure 3). Furthermore, sensitivity analysis suggested the aggregated mortality was not substantially influenced. As the energy intake was tremendously varying from study to study, subgroup analysis

was performed according to the percentage of the target energy achieved and showed that mortality was decreased in the low-energy subgroup, fed 33.3 to 66.6% of goal energy (RR 0.82; 95% CI 0.68-0.98; p=0.03). (Figure 4)

Meta-analysis of secondary outcomes

Infectious complications

For the eight studies with 2,880 patients providing data on infectious complications outcomes, our meta-analysis showed an increasing trend in patients receiving LE (RR 1.09; 95% CI 0.95-1.26; p=0.23; I^2=42%; p=0.10).[24,25,27,28,30,32-34] (Figure 5). According to the subgroup analysis of different daily protein intake, high protein intake might attribute to the above results (RR 1.29; 95% CI 1.10-1.53; p<0.01; I^2=0%; p=0.52). Heterogeneity among the subgroups was also different (I^2=88.7%; p=0.003). The aggregated outcome was also influenced by high protein in the subgroup of L-EN versus H-EN (RR 1.25; 95% CI 1.04-1.52; p<0.05; I^2=0%; p=0.41).

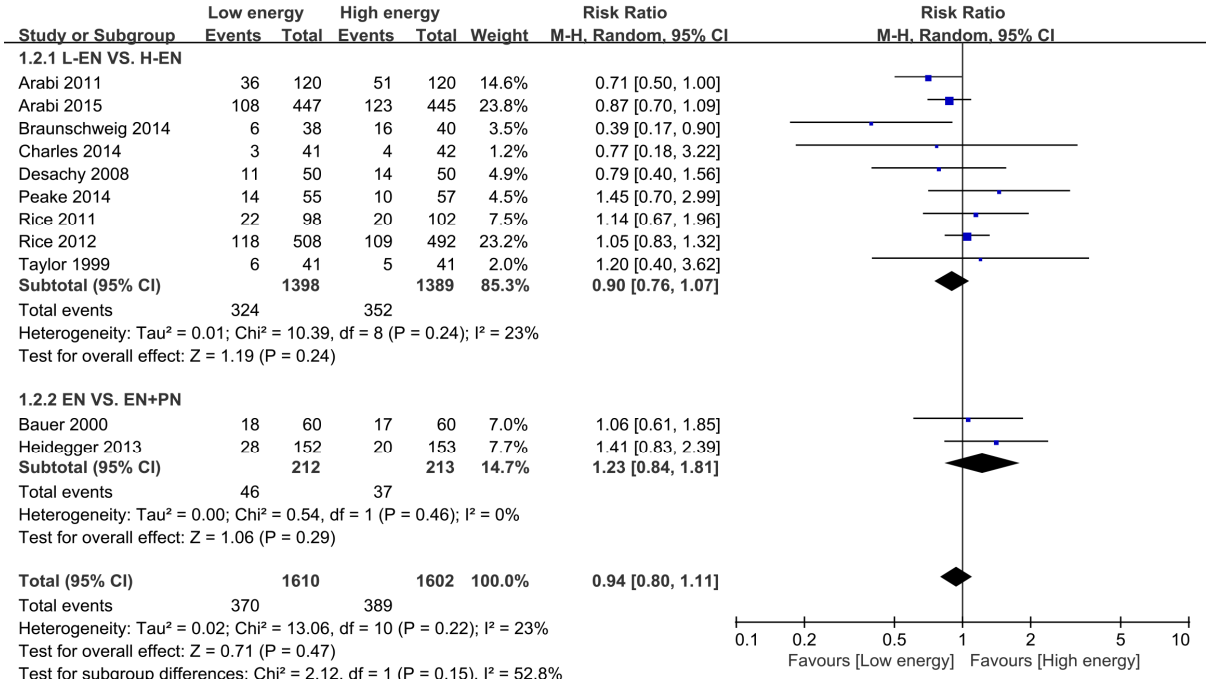

Figure 3. The impact of initial low energy feeding on mortality is shown. MH: Mantel-Haenszel; CI: confidence interval; L-EN: low enteral nutrition; H-EN: high enteral nutrition; EN: enteral nutrition; PN: parenteral nutrition.

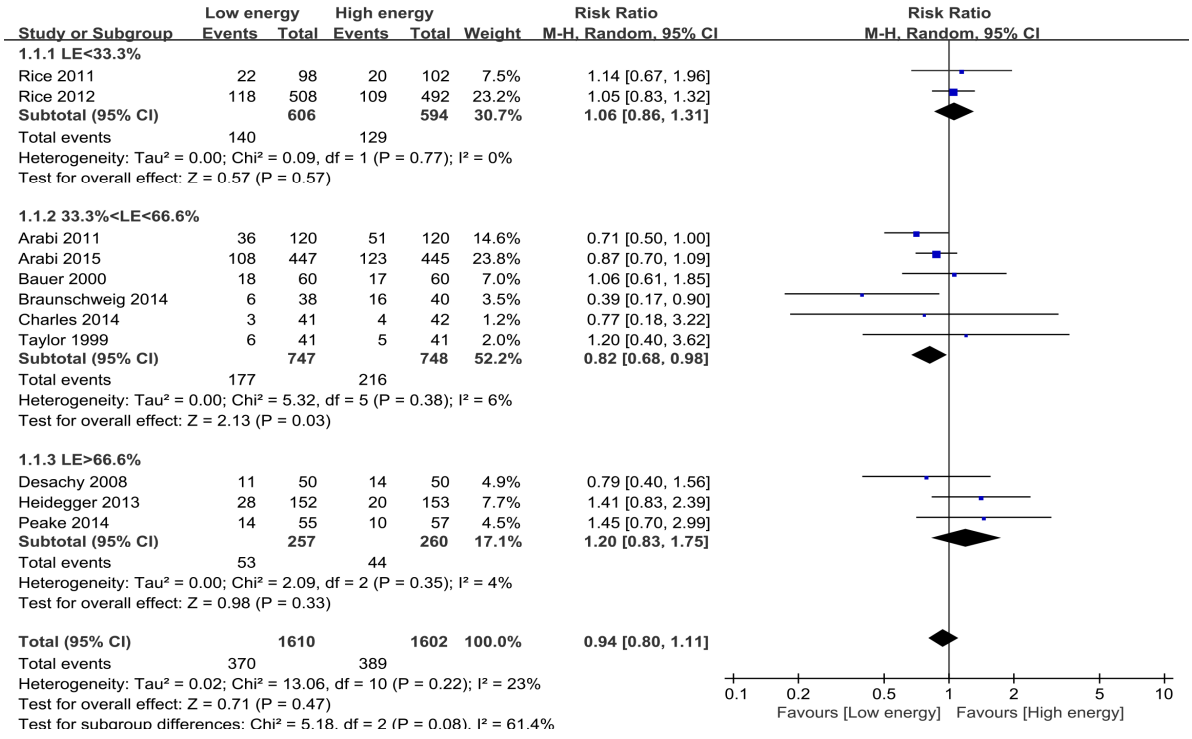

Figure 4. The subgroup analysis of initial low energy feeding on mortality is shown. MH: Mantel-Haenszel; CI: confidence interval; LE: low energy.

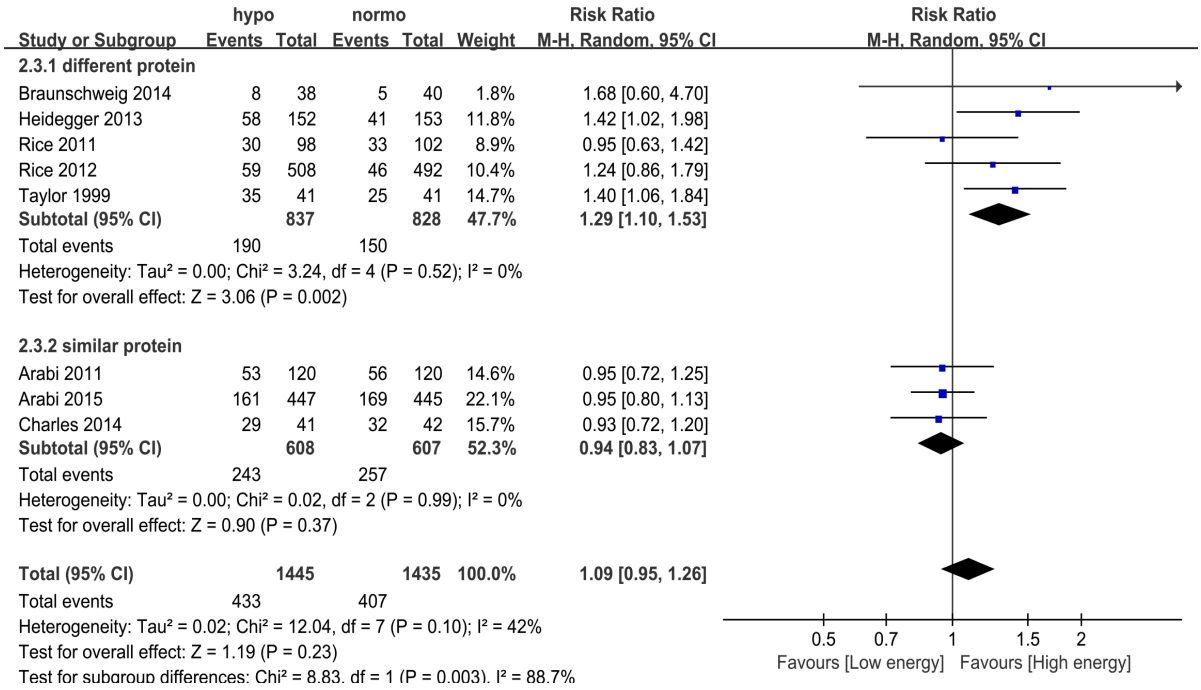

Figure 5. The impact of initial low energy feeding on infectious complications is shown. MH: Mantel-Haenszel; CI: confidence interval; L-EN: low enteral nutrition; H-EN: high enteral nutrition; EN: enteral nutrition; PN: parenteral nutrition.

Pneumonia morbidity

On the basis of the meta-analysis from eight studies with 2,924 participants, no significant difference between groups was observed for pneumonia morbidity (RR 1.04; 95% CI 0.88-1.23; p=0.68).[24-26,28,30,32-34] The test for heterogeneity also proved nonsignificant (I^2=13%; p=0.33).

Length of hospital stay

Pooling the data from six studies with 926 patients (LE=461; HE=465) showed no statistically significant differences between the LE and HE groups (WMD -0.27; 95% CI -3.21 to 3.76; p=0.88).[24,26-30] The test for heterogeneity was not significant (I^2=0%; p=0.75). On sensitivity analysis, no individual study substantially influenced the aggregated RR for LOS-HOS.

Length of ICU stay

We compared the LOS-ICU between two groups with a total of 926 patients from six studies (LE=461 and HE=465). The LE group patients had a mean LOS-ICU of 0.32 days less than that of the HE patients, but difference was not statistically significant (WMD -0.32; 95% CI -1.81 to 1.16; p=0.46).[24,26-30] The result of the test for heterogeneity was also not significant (I^2=0%; p=0.52). On sensitivity analysis excluding any of the studies, the aggregated result was still not significant.

Mechanical ventilation days

In the meta-analysis of four studies including 865 participants, MVD was not significantly different for patients in the LE and HE groups (WMD -0.30; 95% CI-1.42 to 0.82; p=0.60).[24,26,30,32] The test for heterogeneity was not significant (I^2=16%; p=0.31). On sensitivity analysis excluding any of the studies, the aggregated result was not substantially influenced.

Gastrointestinal intolerances

For the two studies of 1,232 patients that provided data on gastrointestinal intolerance, meta-analysis showed that patients in lower energy group had less gastrointestinal intolerances. (RR 0.79; 95% CI 0.65-0.97; p=0.02; heterogeneity I^2=0%; p=0.46).[24,25,29]

DISCUSSION

In this meta-analysis of eleven RCTs evaluating the effect of initial low- energy feeding in critically ill adult patients on clinical outcomes, no statistically significant results were observed in mortality, infections, pneumonia morbidity, LOS-HOS, LOS-ICU or MVD when compared with initial high-energy feeding.

Our study is the first meta-analysis of the effect of initial low energy feeding upon clinical outcomes in critically ill adult patients who can tolerate partial EN; however, previous systematic reviews and meta-analyses largely focussed on infants[35] and the comparison between EN and PN[5,36,37] or immunonutrition and standard nutrition.[38,39] A recent meta-analysis was published about initial hypocaloric EN in critical illness, however, it only involved four studies which were focussed on EN rather than initial energy intake.[40] Critically ill patients often do not tolerate initial full feeding EN due to gastrointestinal intolerance. The initial EN attempts do not achieve the estimated nutrient requirements. Some cohort studies demonstrated that long-term LE nutrition support was associated with high risks of mortality and long hospital stay.[14-16] The SPN has been tried to solve the energy deficiency of EN, but the conclusions have not reached a consensus seemingly. In that case, what about initial low energy? Whether the initial LE nutrition support influenced patients' clinical outcomes was still unclear. Recently, relevant large sample multicenter RCT shave been performed,[30,33,41] but more powerful meta-analyses have not been reported.

Although we tried to search all related literature, we noted clear publication bias for LOS-ICU. Nevertheless, the pooled outcome was stable on sensitivity analysis, and, as such, we advise caution in the interpretation of this result; it is worth noting that seven in eleven studies have a high risk of performance bias as a result of research features.[24,25,28-30,32,33] Despite being interested in the influence of nutrition support dose, infusion times differ based on delivery volumes; therefore, blinding participants and personnel to the dose is not possible. Only one of the seven previously mentioned studies avoided detection bias by involving other independent investigators.[30] Both the random effects model and sensitivity analysis were used to draw a conclusion.

Considering the influence of a nutrition regimen, we attempted a subgroup analysis to identify the heterogeneity source. We found no statistically significant difference in overall mortality or infections morbidity once EN was administered to the patients in the two groups. What is interesting is that the use of HE supplementation had a tendency to reduce the infectious complications in patients with critical illnesses. Could we draw a conclusion that HE supplementation was superior to LE supplementation? Unfortunately, the concomitant high protein intake was more likely to have reduced the incidence of infection. If the protein intake was similar between the two groups, the advantage of HE supplementation would be reversed in the subgroup analysis. However, only three studies involved different caloric intakes of supportive isonitrogenous nutrition.[24,25,28] Therefore, additional relevant studies should be performed to confirm this result. Regarding hospital and intensive care unit lengths of stay, five studies reported median time; however, considering the risk of data conversion, we selected other studies that described the mean instead, and our results were not significantly different.

Although three studies reported that low energy EN could decrease the duration of high gastrointestinal residual volumes (GRVs),[29,32,33] the definition of high GRVs differed widely among them. Therefore, we considered the functional outcomes of each such as diarrhea, vomiting and abdominal distention. LE supplementation reduced the gastrointestinal intolerance in only three studies.[24,25,29] Therefore, additional studies should be conducted and the homogeneous report pattern should be advocated.

EN is an important substrate for the vast number of enterocytes and immune cells within the gut-associated lymphoid tissue, crucial in maintaining intestinal mucosal immune function.[7-9,42] Moreover, EN protects the synthesis and secretion of cells associated with intestinal mucosa immunity. A recent study demonstrated that EN promotes the expression of the brush border protein alkaline phosphatase within villus-associated enterocytes, where it alleviates the adverse effects of lipopolysaccharide and bacterial translocation.[43,44] As a result, EN may reduce infectious complications and improve clinical outcomes by reducing inflammation and bacterial translocation.[45] Nevertheless, adverse effects of EN have been reported. One study indicated that nutrition suppresses autophagy (such as the ubiquitin-proteasome pathway), which occurs during nutrient deprivation and is essential for immune response and housekeeping functions. The suppression of such an important process can lead to the accumulation of damaged organelles and toxic proteins.[46-48] As a consequence, EN might improve vital organ failure or more serious conditions in certain patient populations. According to these considerations, once the patients are able to receive EN, similar clinical outcomes could be achieved in both the initial LE and initial HE groups.

The limitation of this meta-analysis is that relatively few available RCTs have investigated the ideal initial energy supplementation in critically ill patients. Furthermore, the significance of meaningful clinical outcomes was limited by the diverse reporting patterns of the results among studies. For instance, there was a tendency for variables to be presented as their median rather than mean values in some studies; these data could not be used in the meta-analysis.[32-34] Uncommon events are more likely to produce erroneous estimated values in a small number of studies. In all but one selected study, the mean patient body mass index was >25, which suggests that the conclusions may not be appropriate for malnourished patients although a few patients in some studies were identified as malnourished.

Although the infection rate had a declining trend in the HE group, considering the influence of protein, the conclusion that the effect of initial HE feeding on clinical outcomes is superior to that of LE feeding for critically ill adult patients who can tolerate EN must be made with caution. In light of the intolerance of initial high dose EN and the higher cost of SPN, critically ill patients who can tolerate EN may be candidates for an initial LE feeding. However, long-term energy deficiencies should be avoided because this meta-analysis only investigated initial LE feeding in non-malnourished patients receiving EN. Finally, these data support the guidelines that suggest delaying PN until day 7-10 in critically ill but non-malnourished and EN-tolerant patients.[2] Our findings are also consistent with those of a recent review regarding the provision and assessment of supportive nutritional therapy in critically ill adult patients.[49]

Conclusions

In summary, this meta-analysis of eleven RCTs demonstrates that mortality, infections, pneumonia morbidity, LOS-HOS, ICU-HOS and MVD were not significantly different between initial LE and HE feeding in non-malnourished critically ill adult patients who can be administered EN. However, the gastrointestinal intolerance was reduced in LE group. The tendency of infections was reduced in the HE group but with regard to the subgroup analysis of similar daily protein intake, the infection morbidity was reversed in HE group. Therefore, if the protein intake is not different, the effect of initial LE feeding on clinical outcomes may be similar to that of HE feeding for critically ill adult patients who can tolerate EN. As the existing meta-analysis methodology has limitations, our results should be interpreted with caution, as more rigorously designed RCTs are required.

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AUTHOR DISCLOSURES

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