

Effect of combined parenteral and enteral nutrition versus enteral nutrition alone for critically ill patients

A systematic review and meta-analysis

Jialing Shi^a, Liying Wei^a, Rongzhi Huang^a, Liang Liao^{b,*}

Abstract

Background and aim: The increased mortality rate and other poor prognosis make malnutrition a serious issue for adult critically ill patients in intensive care unit care. This study was to compare outcomes between combined parenteral and enteral nutrition and enteral nutrition alone for adult critically ill patients.

Materials and methods: The PubMed (June 30st, 2018), EMBASE (June 30st, 2018), and Cochrane library databases (June 30st, 2018) were searched systematically. Randomized controlled trials (RCTs) of comparing combined PN and EN with EN alone were eligible. Relative risks (RRs), mean differences (MDs), and 95% confidence intervals (CIs) were calculated for dichotomous and continuous outcomes.

Results: Eight RCTs involving 5360 patients met the inclusion criteria. Compared with combined PN and EN, fewer respiratory infections (RR, 1.13 [95% CI 1.01–1.25]) and shorter length of days at hospital (MD, 1.83 [95% CI 1.05–2.62]) were observed in EN alone group. And no significant differences were found on hospital mortality (RR, 0.91 [95% CI 0.74–1.12]), length of days in ICU (MD, –0.23 [95% CI –1.79 to 1.32]), duration of ventilatory support (MD, –1.10 [95% CI –3.15 to 0.94]), albumin (MD, –0.04 [95% CI, –0.12 to 0.21]), or prealbumin (MD, –0.77 [95% CI –0.22 to 1.75]) between these 2 groups.

Conclusion: Receiving EN alone decreased the respiratory infections and length of days at hospital for critically ill patients. Combined PN and EN did not add up the potential risk from PN and EN on hospital mortality, length of days in ICU, duration of ventilatory support, albumin, and prealbumin.

Abbreviations: CI = confidence interval, EN = enteral nutrition, ICU = intensive care unit, MD = mean differences, NR = not reported, PN = parenteral nutrition, PN+EN = combined parenteral and enteral nutrition, RCTs = randomized controlled trial, RR = relative risk, SD = standard deviation, STBI = severe traumatic brain injury.

Keywords: enteral nutrition, intensive care unit, meta-analysis, parenteral nutrition

1. Introduction

Nearly 40% of adult critically ill patients have a high risk of malnutrition,^[1] which definitely increases the incidence of mortality and other poor prognosis. As a therapy, nutrition

supplements have become important and necessary. In general, the individual benefits and risks of parenteral nutrition (PN) and enteral nutrition (EN) have been elucidated gradually. Because of cheaper, safer, and more physiologic, EN remains the preferred choice.^[2–4] But EN alone usually is not able to meet the energy targets owing to gastrointestinal intolerance.^[5,6] Although PN overcame this issue, this supplement increased the risk of infectious complications and mortality had been reported in many current guidelines and even recent larger randomized trials.^[7] The increased mortality rate and other poor prognosis make it imperative and urgent to find the most suitable feeding for adult critically ill patients.

Current guidelines recommended starting EN early in ICU and initiating supplemental PN if EN levels are not at goal.^[8–10] There are many published randomized controlled trials (RCTs) regarding the effect of combined parenteral and enteral nutrition (PN+EN). However, potential benefits and possible risks associated with nutrition support (PN+EN versus EN alone) remain unknown. The latest study shown that PN+EN was significantly associated with increasing calorie and protein delivery during the first ICU week compared with EN alone.^[11]

The clinical outcomes may differ between PN+EN and EN alone for critically ill patients in ICU. The objective of our study was to explore the potential effects between PN+EN and EN alone for adult critically ill patients. And the primary outcome was hospital mortality. All included trials would be assessed by

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^a Guangxi Medical University, ^b Department of Orthopedic Trauma and Hand Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.

* Correspondence: Liang Liao, Department of Orthopedic Trauma and Hand Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, China (e-mail: 237586233@qq.com).

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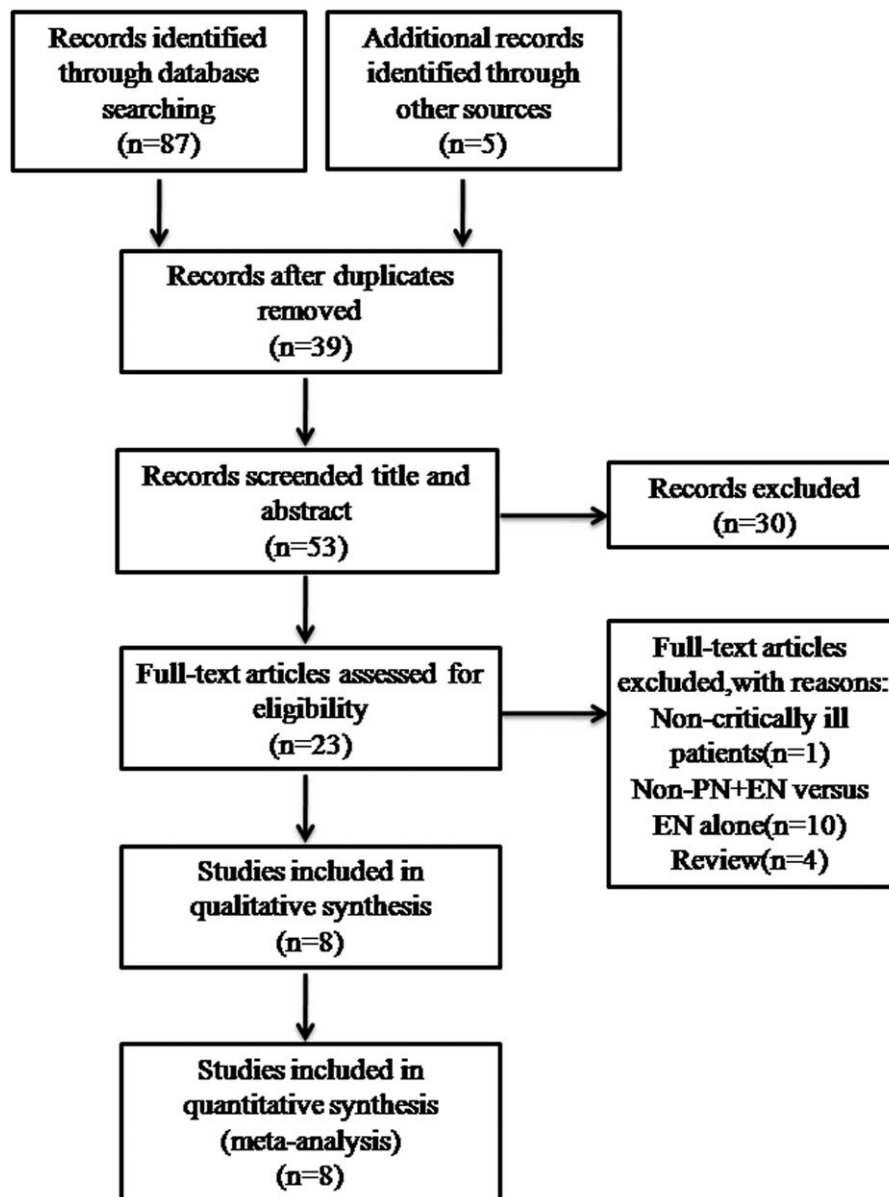


Figure 1. Selection process for randomized controlled trials included in the meta-analysis. EN=enteral nutrition, PN+EN=combined parenteral and enteral nutrition.

Cochrane risk-of-bias tool. Reviewers scored them independently as “high,” “low,” or “unclear” risk. And we undertook a meta-analysis of the latest and most favorable evidence to compare outcomes between 2 groups.

2. Materials and methods

2.1. Literature search

The literature search lasted until June 30, 2018. Reviewers searched the PubMed, EMBASE, and Cochrane library databases systematically by using the following terms: “critical care,” “intensive care,” “critically ill,” “parenteral nutrition,” “supplement parenteral nutrition,” “enteral nutrition,” “enteral feeding,” “randomized controlled trial,” and their associated words.

There was not a limit to the language. RCTs from published systematic reviews or meta-analyses also had access to inclusion.

2.2. Studies selection

RCTs of compared PN+EN with EN alone for adult critically ill patients were eligible. To filter the required articles, the title and abstract were retrospectively reviewed first. And then, we reviewed the full text to verify the qualifications. Inclusion criteria were: target participants were adult critically ill patients in ICU or medical center; RCTs compared PN+EN with EN alone; trials provided clinical outcomes (e.g., mortality). Trials were excluded based on the following exclusion criteria: patients were not considered to be critically ill; trials focused on other nutrition supports; systematic reviews or ongoing trials.

Table 1

Main characteristics of randomized controlled trials included in the meta-analysis of PN + EN versus EN alone for adult critically ill patients.

Author	Country	Population	No. patients	Clinical setting	Time of beginning nutritional support	The proportions of EN and PN in the calories intake	The targets of the artificial nutrition	Nutrition intake		Duration	Main result
								PN + EN	EN alone		
Fan et al ^[11] (2016)	China	Adults	80	Neurological ICU	Within 48 h after admission	NR	105~126 kJ/kg/day	105~126 kJ/kg/day	105~126KJ/Kg per day	20 days	Favors PN + EN
Bauer et al ^[12] (2000)	The United states	Adults	120	ICU	NA	NR	25 kcal/kg/day	24.6 ± 4.9 kcal/kg/day	14.2 ± 6.5 kcal/kg per day	4~7 days	No difference
Wischmeyer et al ^[13] (2017)	Canada, The United States, Belgium, and France	Adults	120	ICU	Within 72 h after admission	NR	BMI < 25: 25 kcal/kg actual weight. BMI > 35: 20 kcal/kg adjusted body weight.	1728 ± 444 kcal/day	1844 ± 420 kcal/day	7 days	Favors PN + EN
Dunham et al ^[14] (1994)	The United states	Adults	24	Shock Trauma Center	24 h After injury	EN = 50% PN = 50%	NR	2240 ± 192 kcal/day	2153 ± 287 kcal/day	7 days	No difference
Hemdon et al ^[15] (1987)	The United States	Adults	28	Burn Center	NR	NR	25 kcal/kg/day + 40 kcal/%TBSA	3431 ± 336 kcal/day (0~3 days); 3977 ± 304 kcal/day (4~7 days)	2159 ± 196 kcal/day (0~3days); 3036 ± 337 kcal/day (4~7days)	10 days	No difference
Huang et al ^[16] (2000)	Taiwan (China)	Adults	40	ICU	NR	NR	Based on physicians' concerns for clinical conditions of patient.	NA	NA	14 days	No difference
Hidegger et al ^[17] (2013)	Switzerland	Adults	305	ICU	4 Days after admission	NR	Woman: 25 kcal/kg of ideal bodyweight a day; Man: 30 kcal/kg of ideal bodyweight a day	28 ± 5 kcal/kg/day	20 ± 7 kcal/kg/day	5 days	Favors PN + EN
Cassier et al ^[18] (2011)	Belgium	Adults	4640	ICU	3 Days after admission	PN < 50%	Maximum: 2880 kcal/day	PN < 50%	NR	NR	Favors late PN + EN

EN = enteral nutrition, ICU = intensive care unit, NR = not reported, PN + EN = combined parenteral and enteral nutrition, TBSA = total body surface area.

2.3. Outcome measures

The primary outcome was hospital mortality because these data were closely related to the prognosis of patients. To reflect the nutritional state, this study extracted respiratory infections, length of days in ICU and at hospital, ventilatory support, albumin, and prealbumin as the secondary outcomes.

2.4. Data extraction

Reviewers extracted the following data independently: first author, publication year, country, population, number of patients, clinical setting, targets of the artificial nutrition, time of beginning nutritional support, the proportions of EN and PN in the calories intake, nutrition intake in PN+EN group and EN alone group, duration, and main result.

2.5. Quality assessment

Reviewers independently evaluated all included trials by Cochrane risk-of-bias tool and scored them as “high,” “low,” or “unclear” risk. The following aspects were taken into consideration: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

2.6. Statistical methods

Statistical analysis was performed using RevMan 5.3. Relative risks (RRs), mean differences (MDs), and 95% confidence intervals (CIs) were calculated for dichotomous (hospital mortality and respiratory infections) and continuous outcomes (length of stay in ICU, ventilatory support, length of stay at hospital, albumin and prealbumin). The χ^2 test was used to quantify statistical heterogeneity. $I^2 < 25\%$ was considered as low-level heterogeneity, 25% to 50% as moderate-level, and $> 50\%$ as high-level heterogeneity. When heterogeneity was present, sensitivity analysis was applied by removing individual studies from the data set and analyzing the effect on the overall results to identify sources of significant heterogeneity. A P value $< .05$ was considered statistically significant.

2.7. Ethical statement

All analyses were based on previous published studies; thus, no ethical approval and patient consent were required.

3. Results

3.1. Study identification and characteristics

A total of 92 records were identified through a complete literature search, of which 39 studies were excluded after duplicates were removed. Reviewers excluded other 30 studies based on titles and abstracts. Full texts of 15 potentially eligible records were reviewed and 8 RCTs met the inclusion criteria.^[11–18] The rest of 8 RCTs were all included in qualitative synthesis (Fig. 1). Finally, 8 RCTs including 5360 adult critically ill patients from multicountry and multicenter were involved in this study (Table 1). The main outcomes of involved RCTs were showed in Table 2.

3.2. Quality assessment

Quality assessment is presented in Figure 2. All RCTs had low risk of random sequence generation, attrition, and reporting bias.

Table 2

Outcomes of randomized controlled trials included in the meta-analysis of PN+EN versus EN alone for adult critically ill patients.

Study	Primary outcome		Secondary outcomes				
	Hospital mortality	Airway/lung infections	Length of days in ICU, days	Ventilatory support, days	Length of days at hospital, days	Albumin, g/dL	Prealbumin, mg/dL
Fan et al ^[11] (2016)	4/40 vs. 12/40	5/40 vs. 7/40	27.61 ± 7.54 vs. 31.42 ± 5.93	8.39 ± 4.67 vs. 12.56 ± 6.12	NR	3.99 ± 0.81 vs. 3.86 ± 0.77	27.74 ± 2.46 vs. 26.84 ± 2.36
Bauer et al ^[12] (2000)	17/60 vs. 18/60	28/60 vs. 23/60	16.9 ± 11.8 vs. 17.3 ± 12.8	11 ± 9 vs. 10 ± 8	31.2 ± 18.5 vs. 33.7 ± 27.7	2.36 ± 0.55 vs. 2.41 ± 0.68	18 ± 10 vs. 19 ± 10
Wischmeyer et al ^[13] (2017)	8/52 vs. 17/73	14/52 vs. 23/73	12.8 (7.9–17.8) vs. 12.6 (8.1–18.7)*	6.5 (3.9–14.1) vs. 8.3 (3.8–13.3)*	23.5 (17.5–34.7) vs. 24.0 (16.6–38.9)*	NR	NR
Dunham et al ^[14] (1994)	3/10 vs. 1/12	NR	NR	NR	NR	NR	NR
Herridon et al ^[15] (1987)	8/13 vs. 8/15	NR	NR	NR	NR	NR	NR
Huang et al ^[16] (2000)	3/18 vs. 4/22	NR	41.9 ± 23.8 vs. 41.6 ± 22.7	55.5 ± 32.2 vs. 47.2 ± 36.8	74.0 ± 40.1 vs. 70.2 ± 22.7	2.7 ± 0.4 vs. 2.4 ± 0.4	14.6 ± 5.6 vs. 12.7 ± 6.5
Heidegger et al ^[17] (2013)	20/153 vs. 28/152	57/153 vs. 60/152	13 ± 10 vs. 13 ± 11	NR	31 ± 23 vs. 32 ± 23	NR	NR
Casaer et al ^[18] (2011)	255/2312 vs. 257/2328	447/2328 vs. 381/2312	4 (2–9) vs. 3 (2–7)*	2 (1–5) vs. 2 (1–5)*	16 (9–29) vs. 14 (9–27)*	NR	NR

Note: Mean ± SD reported for continuous variables. EN = enteral nutrition, ICU = intensive care unit, NR = not reported, PN+EN = combined parenteral and enteral nutrition.

* Data reported as median (Q1–Q3).

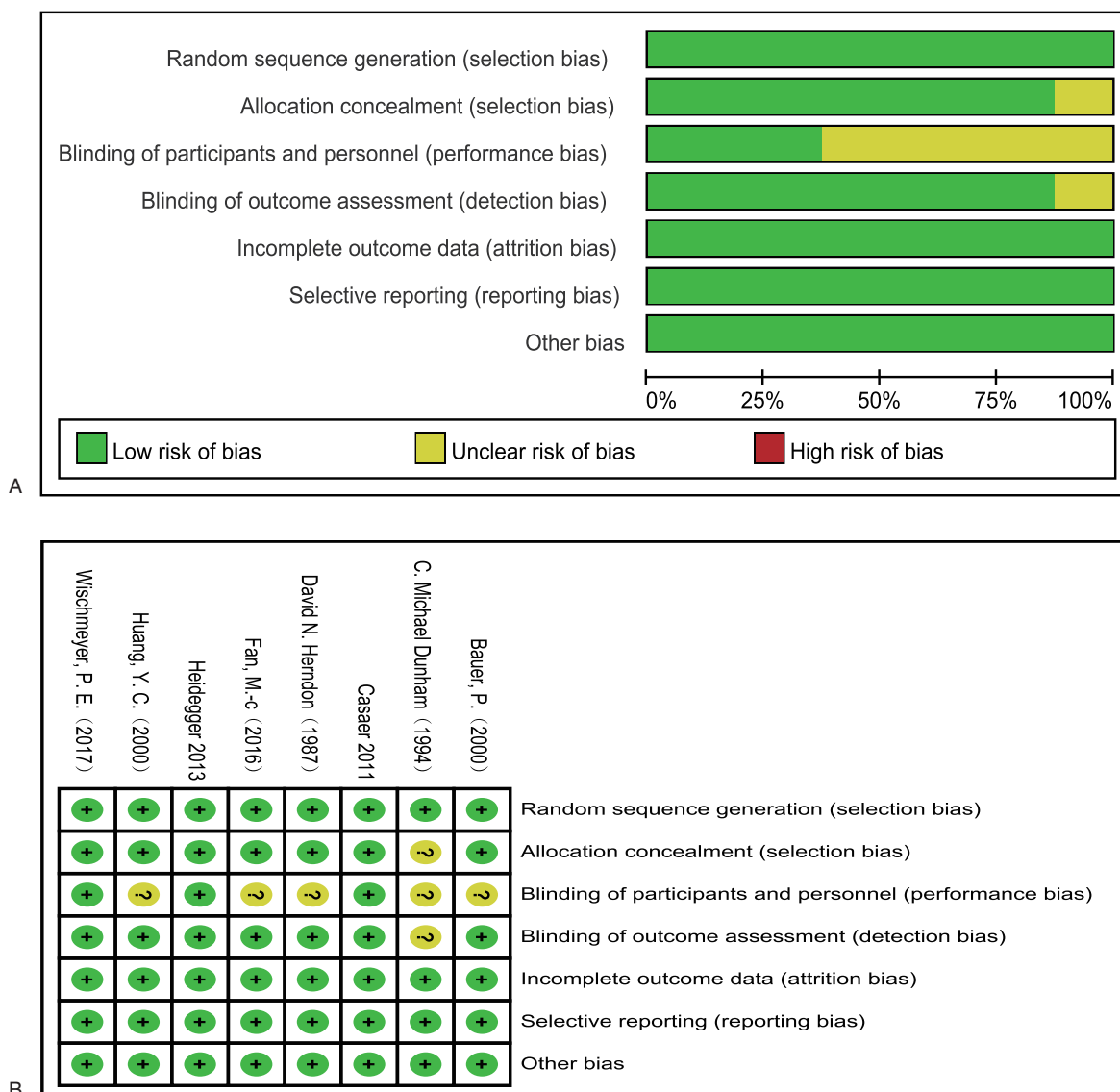


Figure 2. Quality assessment. (A) Risk of bias graph: the author’s judgments about each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: the author’s judgments about each risk of bias item for all included studies.

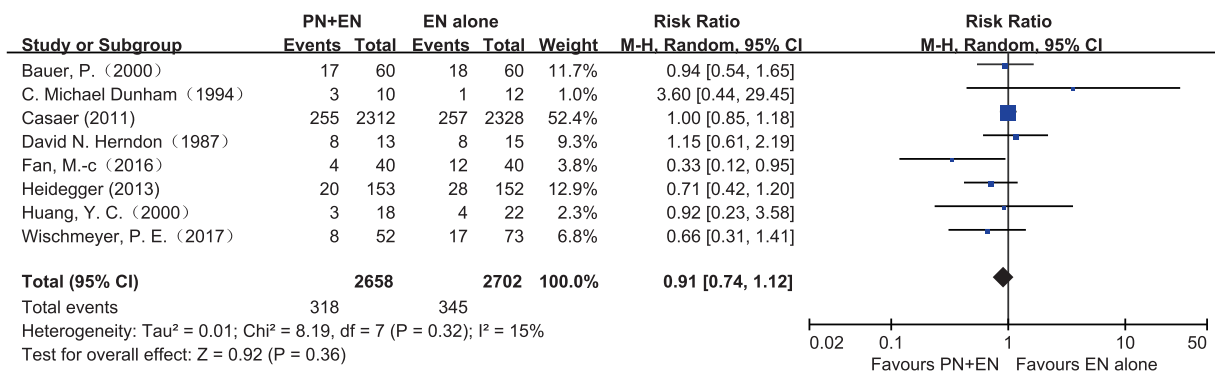


Figure 3. Forest plot showing the effect on hospital mortality comparing PN+EN with EN alone. CI=confidence interval, EN=enteral nutrition, PN+EN=combined parenteral and enteral nutrition.

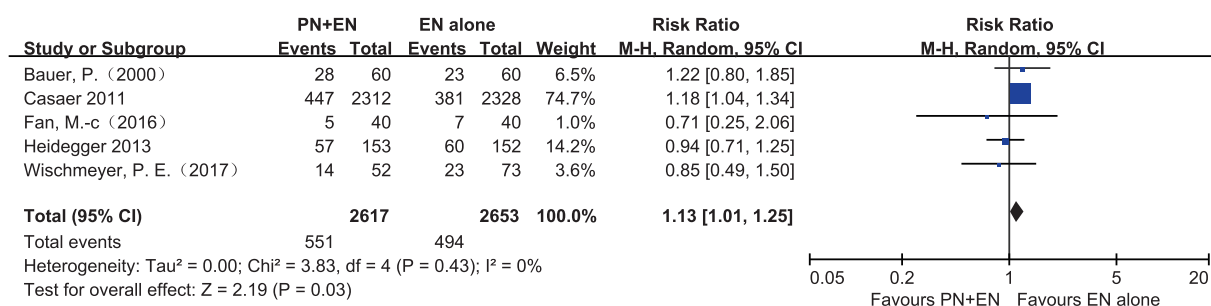


Figure 4. Forest plot showing the effect on respiratory infections comparing PN+EN with EN alone. CI=confidence interval, EN=enteral nutrition, PN+EN=combined parenteral and enteral nutrition.

Five trials represented unknown risk of performance bias. The data of Wischmeyer et al and Casaer et al were included in this study, although length of days in ICU and at hospital, duration of ventilatory support were reported as median (Q1–Q3). In statistical analysis, reviewers regarded the median as the approximate average and calculated the approximate standard deviation (SD) by using the formula $SD = (Q3 - Q1) / 1.35$.^[19]

3.3. Primary outcomes: hospital mortality

All trials reported the mortality between PN+EN and EN alone (Fig. 3). No statistically significant difference was observed on hospital mortality compared PN+EN with EN alone for adult critically ill patients (RR, 0.91 [95% CI 0.74–1.12]).

3.4. Secondary outcomes

Fewer patients in EN alone group acquired the respiratory infections (RR, 1.13 [95% CI 1.01–1.25]) (Fig. 4). Length of days at hospital (MD, 1.83 [95% CI 1.05–2.62]) were shorter in EN alone group (Fig. 5B). The data showed no significant differences on length of days in ICU and duration of ventilatory support (Fig. 5A and C). However, there was high-level heterogeneity in these 2 outcomes ($I^2 = 56%$ on length of days in ICU, $I^2 = 72%$ on duration of ventilatory support). Albumin and prealbumin were similar while comparing PN+EN with EN alone (Fig. 6A and B).

3.5. Sensitivity analysis

The sensitivity analysis was applied by removing individual studies from the data set. As for length of days in ICU, the high-level heterogeneity came from the trial by Fan et al. After removing the trial, a significant decrease on length of days in ICU was observed in EN alone group (MD, 0.98 [95% CI 0.72–1.23]). With regard to duration of ventilatory support, the trial by Fan et al also caused the high-level heterogeneity. In sensitivity analysis, the duration of ventilatory support was similar in the 2 groups.

4. Discussion

This study explored the overall effects of nutrition support (PN+EN vs. EN alone) on clinical outcomes for adult critically ill patients. Finding from this study suggested receiving EN alone significantly decreased the respiratory infections and length of days at hospital for critically ill patients.

Receiving EN contributed to preserving the gastrointestinal function furthest. There were >70% of lymphoid tissues located in the gastrointestinal tract.^[20] Thus, the gastrointestinal tract not only worked as a digestive organ, but also as a primary immune organ. For critically ill patients, EN may exert its roles through the following ways. On one hand, EN helped in maintaining the mechanical barrier of mucosa^[21,22] by keeping the normal structure of intestinal mucosa cells, intercellular junction, and villus height. When EN was initiated, gastric acid, pepsin, and IgA were secreted, which contributed in keeping the balance of biological, immunologic, and chemical barrier of mucosa and holding the growth of intestinal flora.^[21,23] On the other hand, EN has been proved efficient in restoring blood lymphocyte stimulation capacity and dietary fiber could clean up the intestinal tract, promote the refreshment of enterocyte, and maintain the function of the gastrointestinal tract. These may be used to explain the finding that fewer respiratory infections and shorter length of days at hospital were observed in EN alone group for critically ill patients in our study. In sensitivity analysis, significantly decreased length of days in ICU was also observed in EN alone group.

EN has been used widely; however, receiving EN alone has some limitations for critically ill patients obviously. EN alone might be significantly associated with malnutrition. Cahill^[24] reported practitioners are only successfully delivering approximately 59% of prescribed daily calories from EN alone during the first 12 days in ICU. In many guidelines and larger randomized trials, patients could hardly achieve their targets totally by receiving EN alone,^[25–27] and would take a long time to reach it.^[28,29] On the contrary, the nutritional status of critically ill patients will be improved rapidly by receiving PN.^[30–32] Many meta-analyses suggested no differences were found in mortality comparing PN with EN. And new data indicated that the incidence of infectious complications may have reduced with contemporary care in the ICU.^[29,33,34] Moreover, less patients experienced vomiting and diarrhea by PN, and they may feel more comfortable than EN alone.^[35] Owing to the advantages, PN has been utilized clinically 35% to 70%.^[24]

Our study found that early PN+EN did not add up the potential risk compared with EN alone. First, PN+EN are more likely to decrease complications and improve clinical outcomes. PN+EN provide a protective window for gastrointestinal tract to reduce its burden and restore its function. It would help improve the clinical outcomes for critically ill patients. Result here showed that PN+EN has an encouraging trend on reducing mortality and duration of ventilatory support. Second, PN+EN increases protein delivery and decreases malnutrition. Proteins are one of

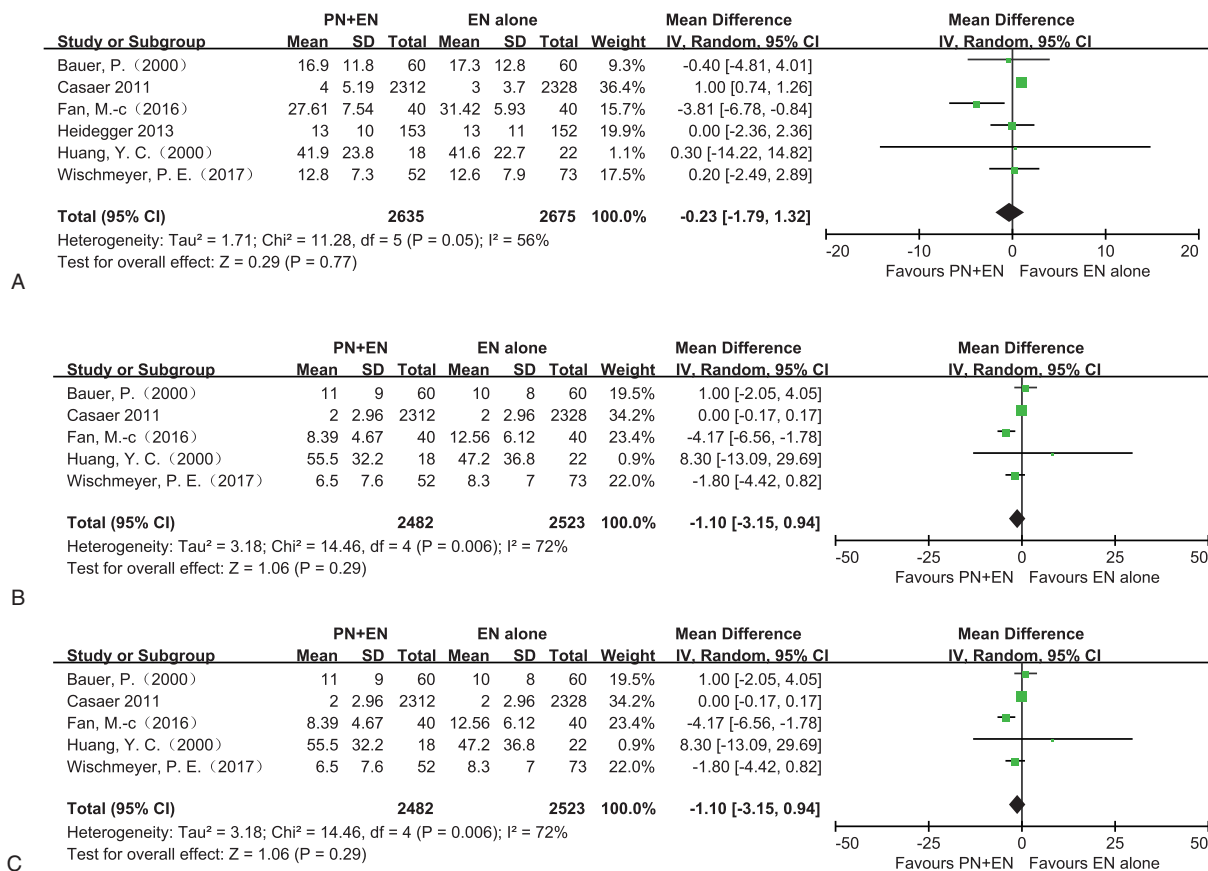


Figure 5. Forest plot showing the effects on length of days in ICU, duration of ventilatory support, and length of days at hospital comparing PN+EN with EN alone. (A) Length of days in ICU. (B) Duration of ventilatory support. (C) Length of days at hospital. CI= confidence interval, EN= enteral nutrition, ICU= intensive care unit, PN+EN=combined parenteral and enteral nutrition, SD=standard deviation.

the major important determinants to survival and recovery of ICU patient, not only to maintain nitrogen balance but also to keep other vital functions. Significantly reduced muscle mass caused by hypercatabolism relates to the increase of complications and mortality. More and more high-quality RCTs revealed that protein intake would hardly reach the standard only by

receiving EN alone.^[36-38] In this study, the levels of albumin and prealbumin were increased by PN+EN, but it did not reach statistical significance.

In sensitivity analysis, the trial by Fan et al caused the high-level heterogeneity on length of days in ICU and duration of ventilatory support. The participants of this trial were patients

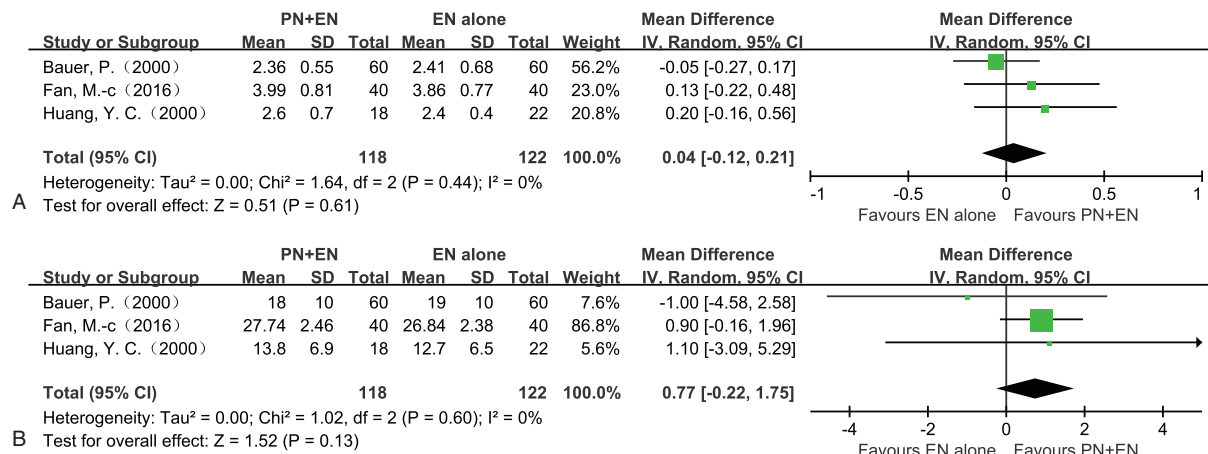


Figure 6. Forest plot showing the effects on biochemical indexes comparing PN+EN with EN alone. (A) albumin. (B) Prealbumin. CI= confidence interval, EN= enteral nutrition, PN+EN=combined parenteral and enteral nutrition, SD=standard deviation.

with severe traumatic brain injury (STBI), whom Glasgow coma scale score was between 6 and 8 and nutritional risk screening ≥ 3 . Compared with other ICU patients, the STBI patients were more severe and acquired longer length of days in ICU and duration of ventilatory support.

Several meta-analyses comparing nutrition support of ICU patient have been published. Differently, most of them focused on comparing PN alone with EN alone.^[25,39,40] However, no significant overall difference was reported in mortality between PN alone and EN alone yet. As a potential nutrition support, PN + EN has been studied in many RCTs. Last few years, rare meta-analyses focusing on PN + EN versus EN alone were published. The latest one was published in 2004 by Dhaliwal et al.^[41] They recommended that PN should be added when reaching the maximum utilization of receiving EN alone. However, the study only enrolled 233 patients and had many incomplete outcome data that would make the outcomes more prone to be influenced by a potential publication bias. In contrast to previous meta-analyses, this study involved >5360 patients from multicountry and multicenter. This study is the latest and most powerful to explore the overall effect of PN + EN versus EN alone on clinical outcomes. And taking the results into consideration, early PN + EN and EN alone had the similar risk on prognosis.

This study also has some limitations. First, albumin and prealbumin were used to assess the nutritional state of critically ill patients in this study. However, NRS 2002 and NUTRIC score recommended by Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition (SCCM/ASPEN) seem to be more objective and directed.^[42] Second, this study is a lack of caloric intake and long-term functional outcomes, which are considered as the better indexes.^[43] Last, there were some missing data in some included RCTs. And the rate of nosocomial pneumonia and ventilator-associated pneumonia cannot be shown independently. Next, we will expand the searching scope and collect more data for further analysis.

5. Conclusion

In general, receiving EN alone decreased the respiratory infections and length of days at hospital for critically ill patients. Our study inferred that combined PN and EN did not add up the potential risk from PN and EN on hospital mortality, length of days in ICU, duration of ventilatory support, albumin, and prealbumin. To demonstrate the most appropriate time and program, the further large-scale and well-designed RCTs are needed.

Author contributions

Data curation: Liying Wei.

Methodology: Rongzhi Huang.

Project administration: Liang Liao.

Software: Rongzhi Huang.

Visualization: Jialing Shi.

Writing – original draft: Jialing Shi.

Writing – review & editing: Liang Liao.

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