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Effect of combined parenteral and enteral nutrition for patients with a critical illness
A meta-analysis of randomized controlled trials

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Abstract

Background: Whether combined parenteral nutrition (PN) and enteral nutrition (EN) is superior to EN alone remains controversial.

Objectives: This study aimed to evaluate the efficacy and safety of combined PN and EN versus EN alone for critically ill patients based on published randomized controlled trials (RCTs).

Data sources: Studies designed as RCTs evaluating the treatment effectiveness of combined PN and EN versus EN alone for critically ill patients were identified from PubMed, Embase, and the Cochrane Library from inception to April 2019.

Methods: The pooled relative risks and weighted mean differences with corresponding 95% confidence intervals were calculated using the random-effects model. Twelve RCTs recruiting a total of 5609 adults and 1440 children were selected for the final meta-analysis.

Results: The summary relative risks indicated that combined PN and EN was not associated with the risk of all-cause mortality, respiratory infection, urinary tract infection, and nutrition-related complications. Moreover, combined PN and EN was associated with longer hospital stay and higher albumin and prealbumin levels compared with EN alone. No significant differences were, however, found between combined PN and EN and EN alone in terms of ventilatory support, intensive care unit stay, and transferrin and C-reactive protein levels.

Conclusions: This study showed that combined PN and EN significantly increased hospital stay duration and albumin and prealbumin levels compared with EN alone for critically ill patients. Large-scale RCTs should be conducted to compare the treatment effectiveness of combined PN and EN versus EN alone for critically ill patients due to a specific cause.

Abbreviations: CI = confidence interval, CRP = C-reactive protein, EN = enteral nutrition, PN = parenteral nutrition, RCT = randomized controlled trial, RR = relative risk, WMD = weighted mean difference.

Keywords: efficacy and safety, enteral nutrition, meta-analysis, parenteral nutrition

1. Introduction

The body's nutritional requirements increase in situations such as critical illnesses, stress, surgery, catabolic state, and negative nitrogen balance. Moreover, prolonged bed rest and inactivity can induce a negative nitrogen balance accentuated by exogenous steroids.[1,2] Patients with critical illness, trauma, and sepsis are in a hypermetabolic state, which, combined with bed rest and inactivity, result in the progression of malnutrition. Furthermore, critically ill patients are always unconscious and unable to feed themselves or receive oral nutritional support, leading to increased susceptibility to malnutrition. Malnutrition can induce mortality and morbidity besides susceptibility to infectious and noninfectious complications.[3,4]

Total parenteral nutrition (PN) was widely used in the 1970s and 1980s to counteract the metabolic problems caused by illnesses.[5] Moreover, enteral nutrition (EN) was introduced as a means to reduce mucosal atrophy and increase intestinal permeability with a reduction in gut translocation and septic complications.[6] Nowadays, the frequencies of PN and EN are 12% to 71% and 33% to 92%, respectively, in critically ill patients needing nutritional support.[7–9] Several meta-analyses compared the treatment effectiveness of PN with EN for patients with a critical illness. Yao et al[10] conducted a meta-analysis of 5 randomized controlled trials (RCTs) and found that critically ill patients with severe acute pancreatitis who received PN were associated with a greater risk of all-cause mortality and multiple-organ failure. Li et al found that the risk of all-cause mortality, pancreatic infection and related complications, organ failure, and surgical intervention significantly reduced in patients with severe acute pancreatitis who received EN compared with those who received PN. Moreover, EN was associated with shorter hospital stay compared with PN.[11] Zhang et al conducted a meta-analysis of 23 RCTs involving 6478 critically ill patients and

found no significant differences between PN and EN in terms of the risk of all-cause mortality and organ failure. Moreover, EN was associated with lower bloodstream infections and shorter hospital stay, and significantly increased the risk of gastrointestinal complications.[12] Whether combined PN and EN was, however, superior to EN alone for critically ill patients remained controversial. Therefore, the current meta-analysis was conducted to compare the treatment effectiveness of combined PN and EN with EN alone for patients with a critical illness.

2. Methods

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

2.1. Data sources, search strategy, and selection criteria

This meta-analysis was conducted and reported with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] Studies designed as RCTs comparing combined PN and EN with EN alone for critically ill patients were selected for inclusion in the present meta-analysis, and no restrictions were placed on language or publication status (published, in press, or in progress). Electronic searches were carried out in PubMed, Embase, and the Cochrane Library from their inception up to April 2019, and the following search terms were used as combined Boolean operators, free text terms, and thesaurus terms: "critical care" OR "intensive care" OR "critically ill" AND "parenteral" AND "enteral" AND "randomized controlled trials." The reference lists of relevant review and retrieved studies were searched through expert recommendations and hand-searching of citations.

Two investigators independently reviewed the studies for eligibility according to the predefined inclusion criteria, and any conflict was settled by a discussion with an additional investigator. Studies were eligible if they met the following criteria: patients: patient with a critical illness in the intensive care unit (ICU); intervention: combined PN and EN; control: EN; outcomes: primary outcomes including all-cause mortality and respiratory infection, and secondary outcomes including urinary tract infection, nutrition-related complications, ventilatory support, ICU stay, hospital stay, and albumin, prealbumin, transferrin, and C-reactive protein (CRP) levels; and study design: RCT design.

2.2. Data collection and quality assessment

Data were abstracted into predefined tables by 2 investigators and compared. Any disagreements were resolved by discussion with an additional investigator. The collected data included first authors' surname, publication year, country, sample size, population, male, Acute Physiology and Chronic Health Evaluation II score, clinical setting, time of beginning nutritional support, targets of the artificial nutrition, intervention, control, duration, and investigated outcomes. The Jadad scale was used for quality assessment based on randomization (1 or 0), concealment of the treatment allocation (1 or 0), blinding (1 or 0), completeness of the follow-up (1 or 0), and use of intention-to-treat analysis (1 or 0).[14] This scale for individual trials ranged from 0 to 5. The quality assessment was conducted by 2 investigators, and conflicts were settled with the help of an additional author referring to the original study.

2.3. Statistical analysis

The treatment effectiveness was compared between combined PN and EN and EN alone for critically ill patients based on relative risks (RRs) or weighted mean differences (WMDs) with corresponding 95% confidence intervals (CIs) in individual trials. The summary RRs and WMDs with corresponding 95% CIs were calculated for categorical and continuous data using the random-effects model.[15,16] Heterogeneity across included studies was assessed using the I-square and Q statistics, and a P value <.10 indicated significant heterogeneity.[17,18] Sensitivity analyses were performed for outcomes reported in ≥5 studies to assess the influence of a single trial on the overall analysis.[19] Subgroup analyses were conducted for all-cause mortality and respiratory infection based on publication year, sample size, clinical setting, duration of intervention, and study quality. Interaction tests were used to evaluate the difference between the subgroups.[20] Publication biases for outcomes reported in ≥5 studies were assessed using funnel plots and Egger[21] and Begg[22] test results. The inspection levels for pooled results were 2 sided, and a P value <.05 indicated a statistically significant difference. All statistical analyses were carried out using Stata software (version 12.0; Stata Corporation, College Station, TX).

3. Results

3.1. Literature search

The initial electronic searches from PubMed, Embase, and the Cochrane Library yielded 265 records; 231 studies were excluded due to duplication and irrelevant topics. The remaining 34 studies were retrieved for further detailed evaluation, and again 22 studies were excluded due to varied reasons. The remaining 12 RCTs were selected for the final analysis.[23,24] No additional study was identified through manual searches. The results of the study selection process are presented in Figure 1.
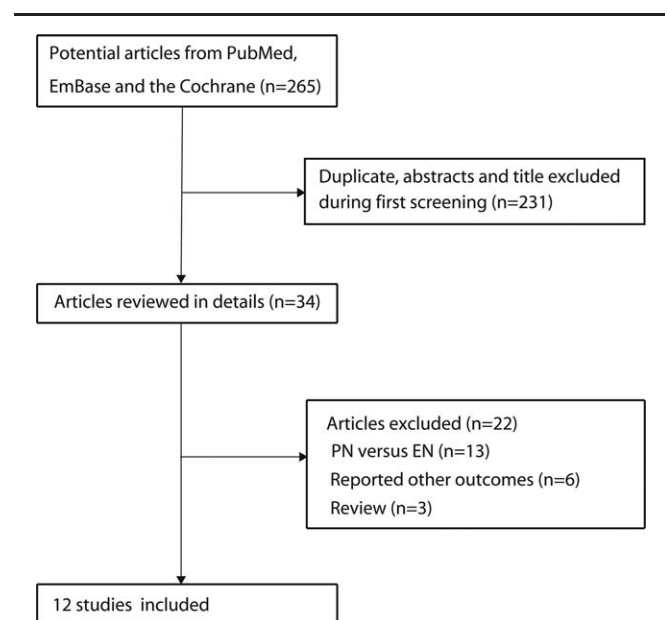

Figure 1. Flow diagram of the literature search and trial selection process. EN = enteral nutrition, PN = parenteral nutrition.

Table 1

Baseline characteristics of studies included in this systematic review and meta-analysis.

Study	Country	Sample size	Population	Male	APACHE II score	Clinical setting	Time of beginning nutritional support	Targets of the artificial nutrition	Intervention	Control	Duration, days	Jadad score
Herndon et al, 1987[23]	US	28	Adults	NA	NA	Burn Center	NA	25 kcal/kg/day + 40 kcal/% total body surface area	3431 ± 336 kcal/day (0–3 days); 3977 ± 304 kcal/day (4–7 days)	2159 ± 196 kcal/day (0–3 days); 3036 ± 337 kcal/day (4–7 days)	10	3
Dunham et al, 1994[24]	US	39	Adults	NA	NA	Shock Trauma Center	24 h after injury	NA	2240 ± 192 kcal/day	2153 ± 287 kcal/day	7	2
Bauer et al, 2000[25]	US	120	Adults	82 (68.3%)	NA	ICU	NA	25 kcal/kg/day	24.6 ± 4.9 kcal/kg/day	14.2 ± 6.5 kcal/kg/day	4–7	4
Huang et al, 2000[26]	China	40	Adults	26 (65.0%)	17.3	ICU	NA	Based on physicians' concerns for the clinical conditions of patients	NA	NA	14	4
Casaer et al, 2011[27]	Belgium	4640	Adults	2972 (64.1%)	23.0	ICU	3 Days after admission	Maximum: 2880 kcal/day	NA	NA	NA	5
Luo et al, 2012[28]	China	60	Adults	NA	NA	Critical Care Medicine	NA	NA	NA	NA	7	3
Heidegger et al, 2013[29]	Switzerland	305	Adults	215 (70.5%)	22.5	ICU	4 Days after admission	Woman: 25 kcal/kg of ideal body weight a day; man: 30 kcal/kg of ideal body weight a day	28 ± 5 kcal/kg/day	20 ± 7 kcal/kg/day	5	4
Fan et al, 2016[30]	China	80	Adults	41 (51.3%)	NA	Neurological ICU	Within 48 h after admission	105–126 kJ/kg/day	105–126 kJ/kg/day	105–126 kJ/kg/day	20	3
Fivez et al, 2016[34]	the Netherlands	1440	Children	830 (57.6%)	NA	Pediatric ICU	Within 24 h after admission	NA	NA	NA	8	4
Wischmeyer et al, 2017[31]	Canada, The United States, Belgium, and France	125	Adults	60 (48.0%)	20.7	ICU	Within 72 h after admission	BMI <25: 25 kcal/kg actual weight BMI >35: 20 kcal/kg adjusted body weight	1728 ± 444 kcal/day	1844 ± 420 kcal/day	7	5
Wu et al, 2017[32]	China	73	Adults	50 (68.5%)	NA	ICU	6 h after the surgery	NA	NA	NA	9	3
Ridley et al, 2018[33]	Australia	99	Adults	70 (70.7%)	18.4	ICU	48–72 h following ICU admission	NA	NA	NA	7	4

APACHE = Acute Physiology and Chronic Health Evaluation II, ICU = intensive care unit.
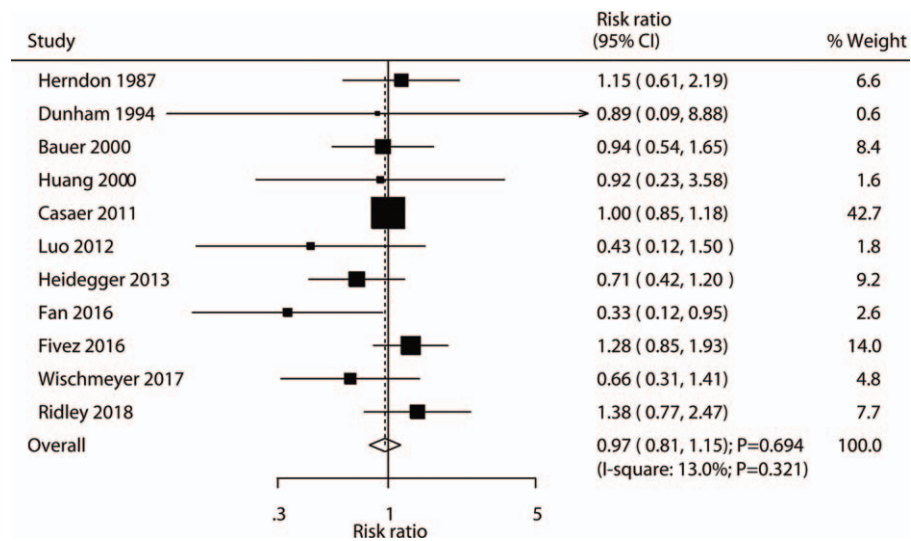
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Figure 2. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on the risk of all-cause mortality. CI = confidence interval.

3.2. Study characteristics

Of the 12 RCTs, 11 trials included critically ill adult patients[23–33] and 1 trial included children with a critical illness.[34] These studies recruited a total of 5609 adults and 1440 children. The sample size ranged from 28 to 4640, and the duration of intervention ranged from 4 to 20 days. Nine studies recruited patients in the ICU, and the remaining 3 studies recruited patients at other medical centers. The study quality was assessed using the Jadad scale. Two trials had a score of 5, 5 had a score of 4, 4 had a score of 3, and the remaining 1 had a score of 2 (Table 1).

3.3. Primary outcomes

Data for the effect of combined PN and EN versus EN alone on the risk of all-cause mortality were available in 11 RCTs. Overall, no significant difference was found between the groups in terms of the risk of all-cause mortality (RR: 0.97; 95% CI: 0.81–1.15; $P = .694$; Fig. 2) and unimportant heterogeneity among the included trials. The sensitivity analysis indicated that the pooled conclusion was not altered by sequentially excluding individual trials Supplemental Digital Content (Figs. S1–S6, http://links. lww.com/MD/D606). The results of subgroup analyses were consistent with overall analyses in all subsets (Table 2). No

Table 2

Subgroup analyses for all-cause mortality and respiratory infection.

Outcomes	Variable	Group	Number of trials	RR and 95% CI	P	Heterogeneity (%)	P value for heterogeneity	P value between the subgroups
All-cause mortality	Publication year	Before 2010	4	1.02 (0.68–1.51)	.940	0.0	.966	.883
		2010 Or after	7	0.91 (0.69–1.19)	.480	46.4	.082	
	Sample size	≥100	5	0.98 (0.85–1.14)	.834	3.4	.387	1.000
		<100	6	0.86 (0.52–1.41)	.546	34.7	.176	
	Clinical setting	ICU	8	0.96 (0.78–1.18)	.690	26.7	.216	1.000
		Non-ICU	3	0.91 (0.49–1.68)	.758	8.0	.337	
	Duration, day	≥10.0	3	0.74 (0.31–1.73)	.486	55.8	.104	1.000
		<10.0	7	0.96 (0.74–1.26)	.790	15.0	.315	
	Study quality	High	7	1.00 (0.88–1.15)	.963	0.0	.502	.446
		Low	4	0.64 (0.30–1.38)	.254	46.2	.134	
Respiratory infection	Publication year	Before 2010	1	1.22 (0.80–1.85)	.358	–	–	.800
		2010 or after	7	1.07 (0.82–1.39)	.636	58.9	.024	
	Sample size	≥100	5	1.18 (0.95–1.46)	.140	55.7	.060	.055
		<100	3	0.64 (0.35–1.17)	.149	0.0	.380	
	Clinical setting	ICU	7	1.16 (0.96–1.40)	.133	39.1	.131	.028
		Non-ICU	1	0.42 (0.17–1.04)	.060	–	–	
	Duration, day	≥10.0	1	0.71 (0.25–2.06)	.534	–	–	.586
		<10.0	6	1.07 (0.75–1.52)	.722	63.2	.018	
	Study quality	High	5	1.18 (0.95–1.46)	.140	55.7	.060	.055
		Low	3	0.64 (035–1.17)	.149	0.0	.380	

CI = confidence interval, ICU = intensive care unit, RR = relative risk.
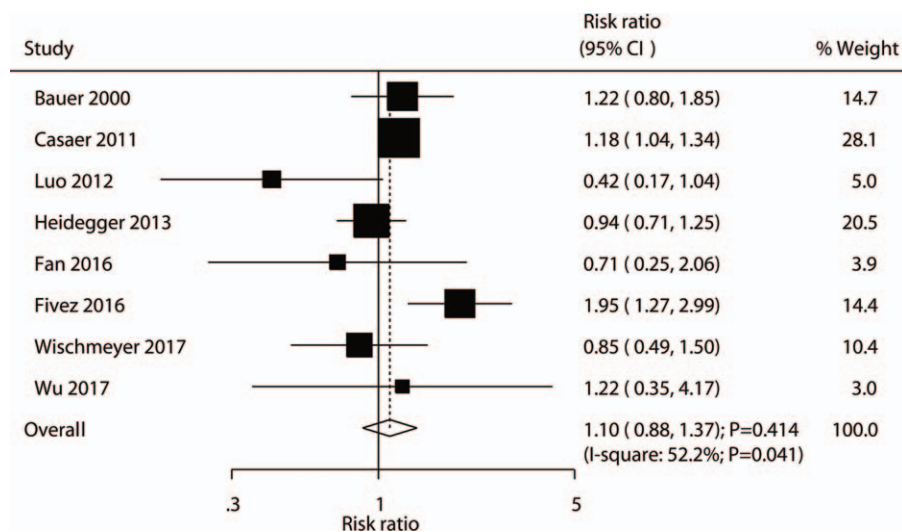
Figure 3. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on the risk of respiratory infection. CI = confidence interval.

evidence of publication bias was detected for all-cause mortality (*P* value for Egger: .232; *P* value for Begg: .350; Supplemental Digital Content Figs. S7–S12, http://links.lww.com/MD/D607).

Data for the effect of combined PN and EN versus EN alone on the risk of respiratory infection was available in 8 RCTs. Combined PN and EN was not associated with the risk of respiratory infection compared with EN (RR: 1.10; 95% CI: 0.88–1.37; *P* = .414; Fig. 3), and significant heterogeneity was observed among the included trials. This conclusion was stable and not affected by removing any particular trial Supplemental Digital Content (Figs. S1–S6, http://links.lww.com/MD/D606). The results of subgroup analyses indicated that sample size, clinical setting, and study quality could affect the treatment effect of combined PN and EN versus EN alone on the risk of respiratory infection, which were consistent with the results of overall analysis (Table 2). No significant publication bias was observed for respiratory infection (*P* value for Egger: .439;

P value for Begg: .711; Supplemental Digital Content Figs. S7–S12, http://links.lww.com/MD/D607).

3.4. Secondary outcomes

Data for the effect of combined PN and EN versus EN alone on the risk of urinary tract infection were available in 5 RCTs, and no significant difference was found between the groups in terms of the risk of urinary tract infection (RR: 1.33; 95% CI: 0.81–2.17; *P* = .261; Fig. 4). Moderate heterogeneity was observed among the included trials. The results of the sensitivity analysis indicated that the pooled conclusion was stable and not changed by sequentially excluding specific trials Supplemental Digital Content (Figs. S1–S6, http://links.lww.com/MD/D606). No significant publication bias was detected (*P* value for Egger: .328; *P* value for Begg: .221; Supplemental Digital Content Figs. S7–S12, http://links.lww.com/MD/D607). Moreover, combined
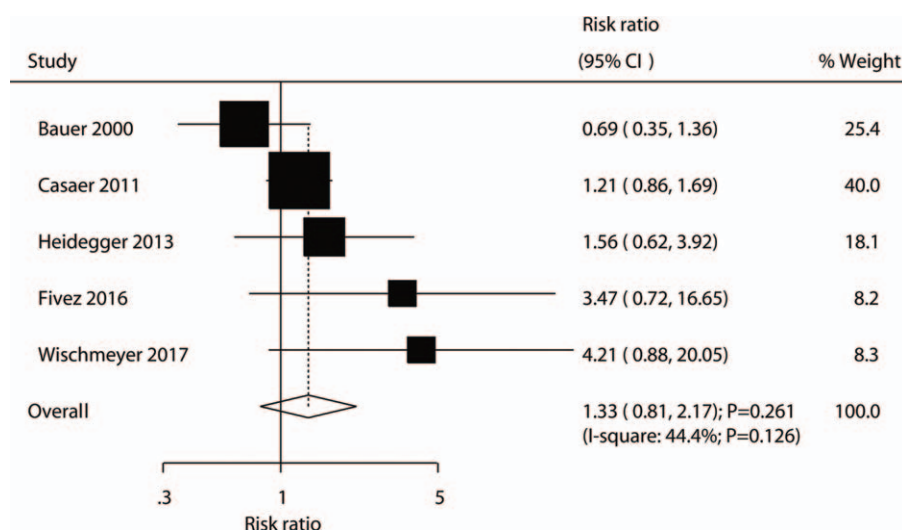

Figure 4. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on the risk of urinary tract infection. CI = confidence interval.
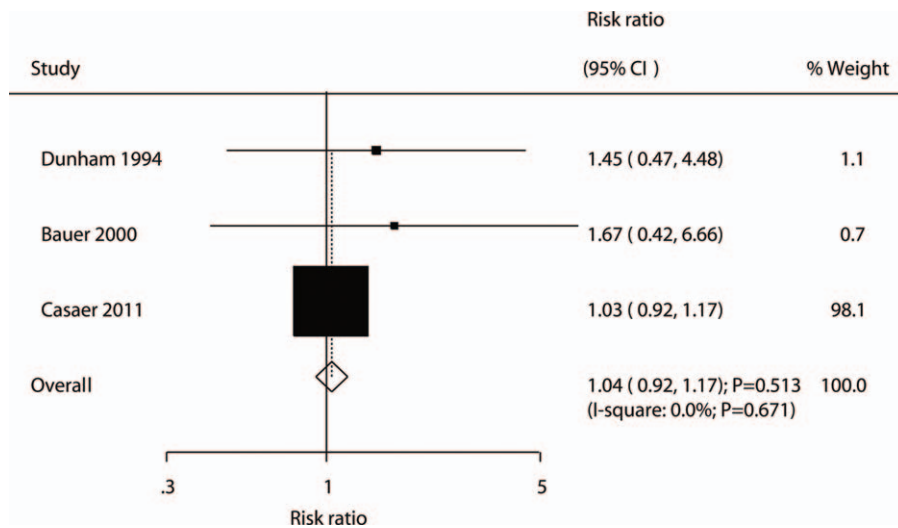
Figure 5. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on the risk of nutrition-related complications. CI = confidence interval.

PN and EN was not associated with the risk of nutrition-related complications (RR: 1.04; 95% CI: 0.92–1.17; $P = .513$; Fig. 5).

Data for the effect of combined PN and EN versus EN alone on the duration of ventilatory support were available in 8 RCTs. Overall, no significant difference was found between combined PN and EN and EN alone in terms of ventilatory support (WMD: –0.05; 95% CI: –1.25–1.16; $P = .938$; Fig. 6), and significant heterogeneity was observed among the included trials. The sensitivity analysis indicated that the conclusion was not altered by excluding any particular trial Supplemental Digital Content (Figs. S1–S6, http://links.lww.com/MD/D606). No significant publication bias for ventilatory support was observed (P value for Egger: .539; P value for Begg: .536; Supplemental Digital Content Figs. S7–S12, http://links.lww.com/MD/D607).

Data for the effect of combined PN and EN versus EN alone on the duration of ICU stay were available in 8 RCTs. Combined PN and EN was not associated with ICU stay compared with EN alone (WMD: 0.47; 95% CI: –0.63 to 1.57; $P = .404$; Fig. 7), and significant heterogeneity was observed among the included trials. The results of sensitivity analyses were stable and not altered by sequential excluding individual trials Supplemental Digital Content (Figs. S1–S6, http://links.lww.com/MD/D606). No significant publication bias was detected for ICU stay (P value for Egger: .261; P value for Begg: .266; Supplemental Digital Content Figs. S7–S12, http://links.lww.com/MD/D607).

Data for the effect of combined PN and EN versus EN alone on the duration of hospital stay were available in 8 RCTs. Combined PN and EN was associated with longer hospital stay compared with EN (WMD: 1.53; 95% CI: 0.02–3.04; $P = .047$; Fig. 8), and significant heterogeneity was observed among the included trials. The results of the sensitivity analysis indicated that the conclusion was variable due to marginal 95% CI Supplemental Digital Content (Figs. S1–S6, http://links.lww.com/MD/D606). No significant publication bias was detected (P value for Egger:
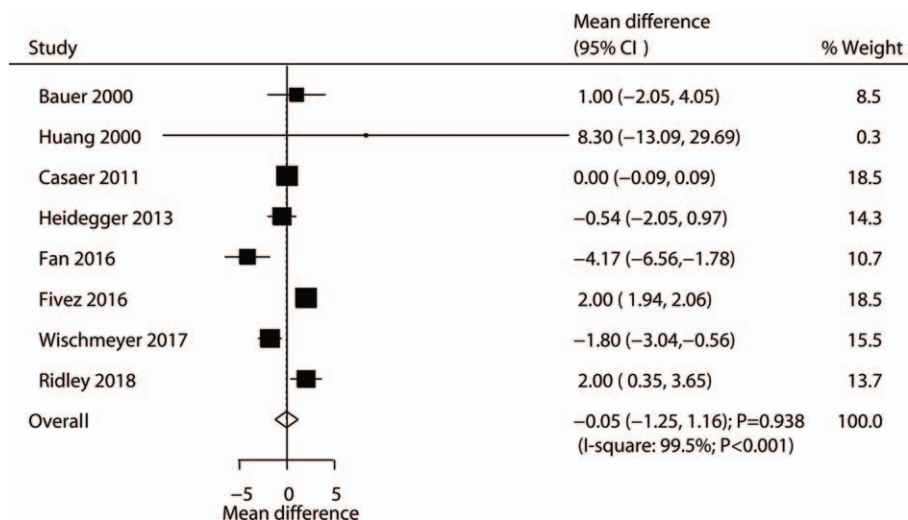

Figure 6. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on ventilatory support. CI = confidence interval.
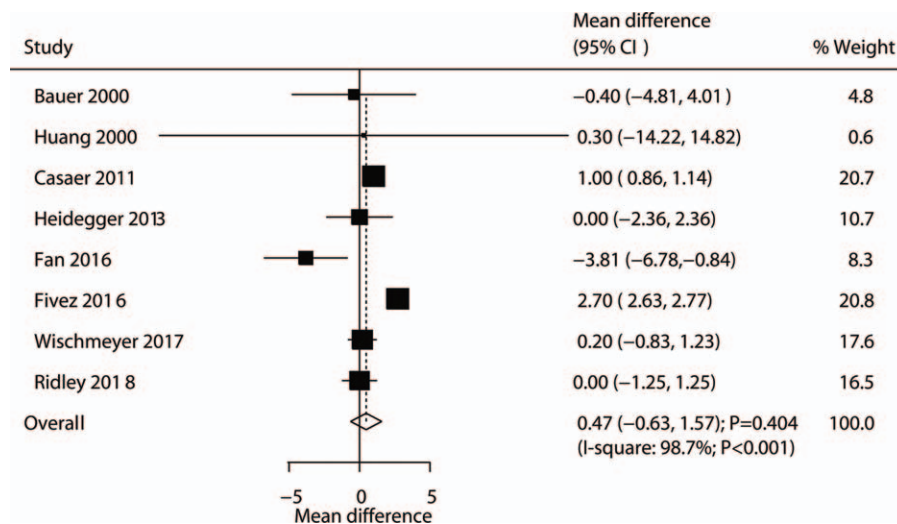
Figure 7. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on intensive care unit (ICU) stay. CI = confidence interval.

.090; *P* value for Begg: .266; Supplemental Digital Content Figs. S7–S12, http://links.lww.com/MD/D607).

Three RCTs reported the effect of combined PN and EN on albumin levels; combined PN and EN was associated with high albumin levels compared with EN (WMD: 2.04; 95% CI: 0.53–3.55; *P*=.008; without evidence of heterogeneity; Fig. 9). Moreover, 4 trials investigated the effect of combined PN and EN on prealbumin levels; combined PN and EN significantly increased prealbumin levels compared with EN (WMD: 0.02; 95% CI: 0.00–0.04; *P*=.036; Fig. 10). Significant heterogeneity was noted among the included trials. Furthermore, 3 trials reported the effect of combined PN and EN on transferrin levels; no significant difference was found between the groups in terms of transferrin levels (WMD: 0.44; 95% CI: –0.46–1.34; *P*=.336; Fig. 11), and significant heterogeneity was observed among the included trials. Finally, 3 trials evaluated the effect of combined PN and EN on CRP levels; no significant difference was found

between the groups in terms of CRP levels (WMD: 17.58; 95% CI: –18.73–53.90; *P*=.343; Fig. 12), and significant heterogeneity was observed among the included trials.

4. Discussion

This study included 12 RCTs involving a total of 5609 adults and 1440 children with a critical illness. The results indicated that combined PN and EN was associated with longer hospital stay and higher albumin and prealbumin levels compared with EN. No significant differences were, however, found between combined PN and EN and EN alone in terms of all-cause mortality, respiratory infection, urinary tract infection, nutrition-related complications, ventilatory support, ICU stay, and transferrin and CRP levels. Moreover, the effect of combined PN and EN versus EN alone on respiratory infection was influenced by sample size, clinical setting, and study quality.
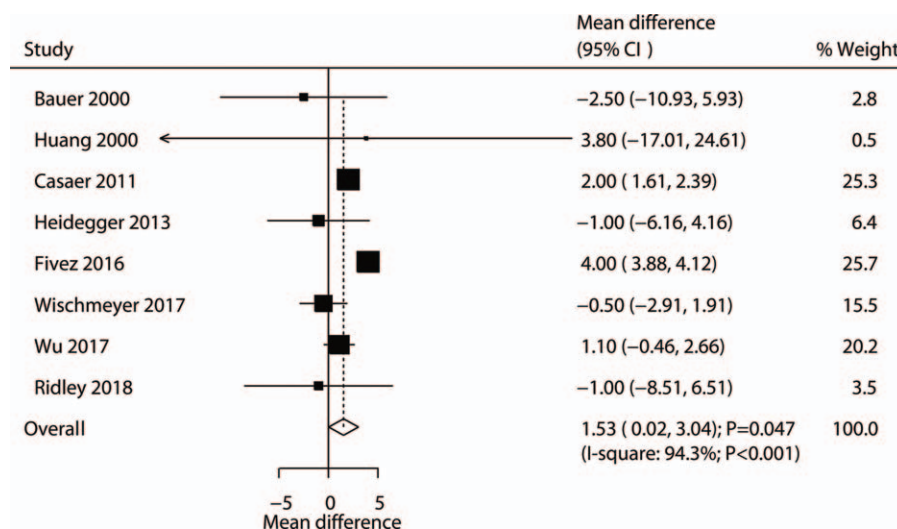

Figure 8. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on hospital stay. CI = confidence interval.
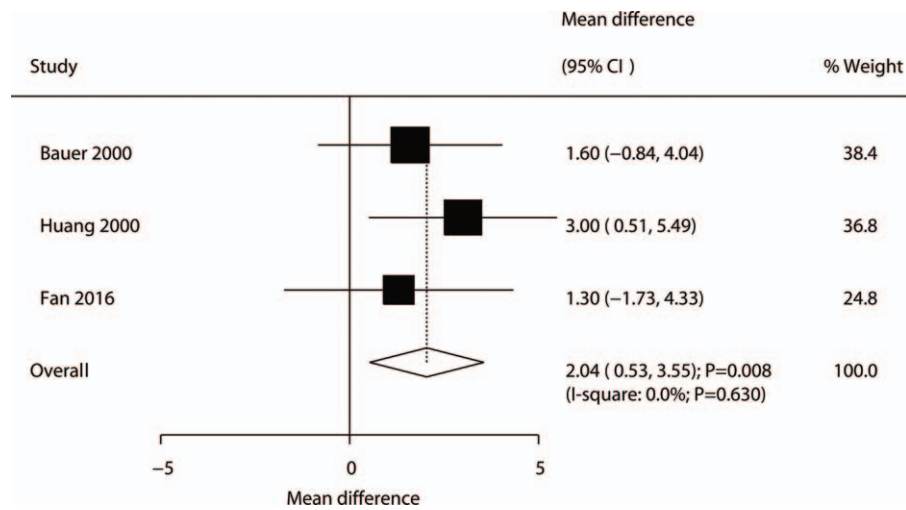
Figure 9. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on albumin levels. CI = confidence interval.

A previous meta-analysis conducted by Wan et al[35] contained 5 RCTs and found early PN, irrespective of whether combined with EN, was not associated with all-cause mortality, whereas it was associated with shorter ventilation duration, and longer hospital stay. This study focused on the whether uses of early PN and the combined with PN and EN versus EN were not addressed. Moreover, Shi et al[36] conducted a meta-analysis of 8 RCTs including 5360 adult patients found that combined PN and EN was associated with increased respiratory infections and longer hospital stay compared with EN alone, whereas no significant differences in hospital mortality, ICU stay, duration of ventilatory support, and albumin and prealbumin levels were found between the groups. Several important studies were, however, not included in this study. [28,32–34] Furthermore, this study just provided the summary results, and the source of heterogeneity was not explored by subgroup analyses. In addition, several important indexes, including urinary tract

infection, nutrition-related complications, and transferrin and CRP levels between combined PN with EN and EN alone were not calculated. Therefore, the present updated meta-analysis was conducted to systematically compare the treatment effectiveness of combined PN and EN with EN alone for critically ill patients. Moreover, subgroup analyses for all-cause mortality and respiratory infection were conducted to evaluate the treatment effectiveness of combined PN and EN versus EN lone in critically ill patients with specific characteristics.

No significant differences in the risk of all-cause mortality and respiratory infection were observed between the groups; these 2 results were stable and not altered by excluding any specific trial. The conclusions of most included trials were similar to those of the overall analyses; however, several trials reported inconsistent results. Fan et al[30] recruited 80 patients with severe traumatic brain injury and found that early combined PN and EN could promote the recovery of immune function, enhance nutritional
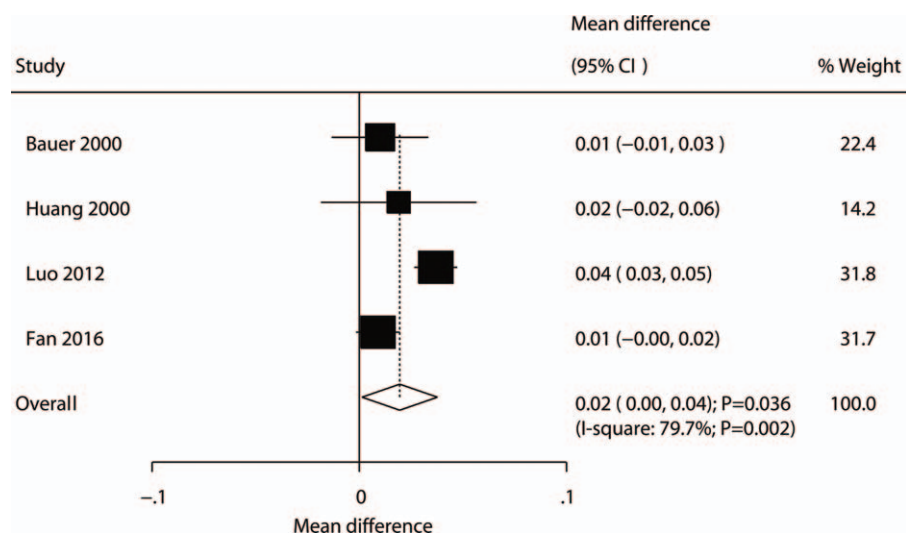

Figure 10. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on prealbumin levels. CI = confidence interval.
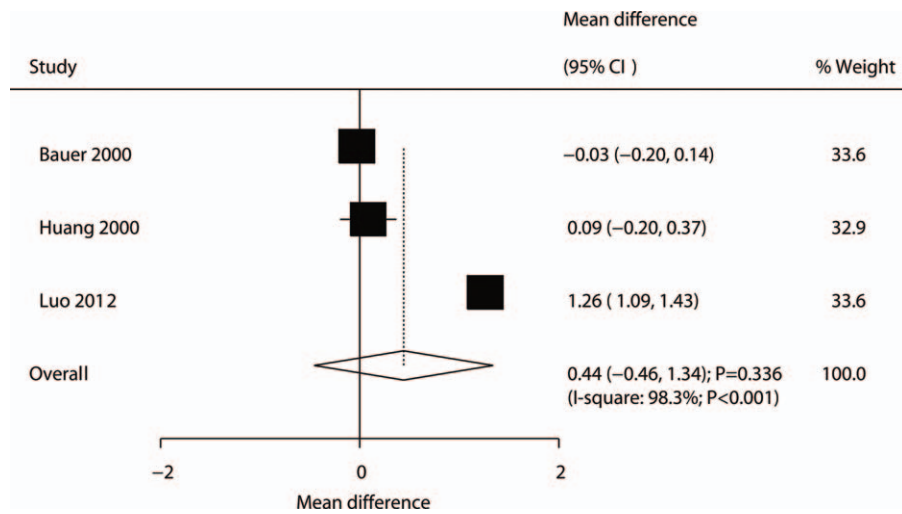
Figure 11. Effect of combined parenteral nutrition (PN) and EN versus EN alone on transferrin levels. CI = confidence interval.

status, reduce complications, and improve the clinical outcomes. The all-cause mortality reported by this trial was, however, 2.4% compared with the value in the overall analysis, thus not affecting the summary results. The study conducted by Casaer et al[27] based on 4640 critically ill adult patients found that combined PN and EN was associated with increased risk of respiratory infection compared with EN. They pointed out that early administration of PN led to increased rates of infection and delayed recovery from organ failure due to the suppression of autophagy, which was associated with inadequate clearance of cell damage and microorganisms.[37–39] Moreover, the study conducted by Fivez et al involving 1440 critically ill children reported that early PN induced a greater risk of respiratory infection. This was probably because early PN was associated with elevated plasma CRP levels, which induced an increased risk of respiratory infection.[40,41] In addition, subgroup analyses

indicated that the risk of all-cause mortality and respiratory infection was stable and not changed based on the predefined factors. Finally, no significant differences in the risk of urinary tract infection and nutrition-related complications were found between combined PN and EN and EN alone. These results might change and hence need further large-scale RCTs for verification.

The results of this study indicated that combined PN and EN was associated with longer hospital stay and high albumin and prealbumin levels compared with EN alone. Two of the included trials indicated that combined PN and EN was related to longer hospital stay compared with EN alone.[27,34] They pointed out that the depletion of lean tissue and underweight patients could affect the length of hospital stay.[42] Moreover, this study showed that combined PN and EN was associated with high albumin and prealbumin levels. The nutritional support treatment should be used according to the actual condition of patients. EN should be
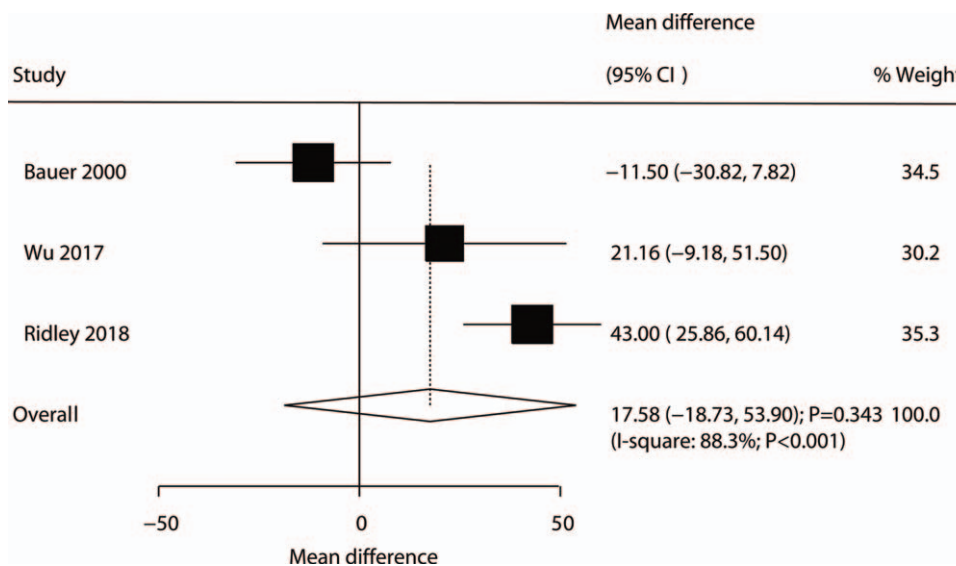

Figure 12. Effect of combined parenteral nutrition (PN) and enteral nutrition (EN) versus EN alone on C-reactive protein (CRP) levels. CI = confidence interval.

used as the first choice under the premise of reaching the nutritional goal, and if EN does not reach the target of nutrition, EN should be employed combined with PN.

Several limitations of this study should be highlighted: it recruited patients under various disease conditions and clinical settings, which affected the prognosis of critically ill patients; most characteristics of patients were not available, which restricted performing more detailed stratified analyses; the source of heterogeneity was not fully interpreted, and the pooled results were unstable; publication bias was inevitable because the analysis was performed based on published RCTs; and the analysis of this study was based on pooled data, which restricted conducting a more detail analysis.

In conclusion, combined PN and EN was associated with longer hospital stay and higher albumin and prealbumin levels compared with EN alone, whereas no significant differences in all-cause mortality, respiratory infection, urinary tract infection, nutrition-related complication, ventilatory support, ICU stay, transferrin, and CRP levels were observed between the groups. Furthermore, large-scale RCTs should be conducted to compare the treatment effectiveness of combined PN and EN with EN alone for critically ill patients due to a specific cause.

Author contributions

Data curation: Yi Luo.
Investigation: Yi Luo.
Methodology: Yi Luo.
Project administration: Yi Luo.
Writing – original draft: Yingxiang Qian.
Writing – review and editing: Yingxiang Qian.

References

[1] Scheld K, Zittermann A, Heer M, et al. Nitrogen metabolism and bone metabolism markers in healthy adults during 16 weeks of bed rest. Clin Chem 2001;47:1688–95.

[2] Ferrando AA, Stuart CA, Sheffield-Moore M, et al. Inactivity amplifies the catabolic response of skeletal muscle to cortisol. J Clin Endocrinol Metab 1999;84:3515–21.

[3] Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003;22:235–9.

[4] Mogensen KM, Robinson MK, Casey JD, et al. Nutritional status and mortality in the critically ill. Crit Care Med 2015;43:2605–15.

[5] Suchner U. The 1996 Nestle International Clinical Nutrition Award for Enteral Nutrition. "Enteral versus parenteral nutrition: effects on gastrointestinal function and metabolism": background. Nutrition 1998;14:76–81.

[6] Heyland DK, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA 1998;280: 2013–9.

[7] Payne-James JJ, De Gara CJ, Grimble GK, et al. Artificial nutrition support in hospitals in the United Kingdom-1991: second national survey. Clin Nutr 1992;11:187–92.

[8] Hill SA, Nielsen MS, Lennard-Jones JE. Nutritional support in intensive care units in England and Wales: a survey. Eur J Clin Nutr 1995;49: 371–8.

[9] Lipman TO. Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. JPEN J Parenter Enteral Nutr 1998;22:167–82.

[10] Yao H, He C, Deng L, et al. Enteral versus parenteral nutrition in critically ill patients with severe pancreatitis: a meta-analysis. Eur J Clin Nutr 2018;72:66–8.

[11] Li W, Liu J, Zhao S, et al. Safety and efficacy of total parenteral nutrition versus total enteral nutrition for patients with severe acute pancreatitis: a meta-analysis. J Int Med Res 2018;46:3948–58.

[12] Zhang G, Zhang K, Cui W, et al. The effect of enteral versus parenteral nutrition for critically ill patients: a systematic review and meta-analysis. J Clin Anesth 2018;51:62–92.

[13] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[14] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–2.

[15] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[16] Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making 2005;25:646–54.

[17] JJ D, JPT H, DG A. Higgins J, Green S. Analyzing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Inter-ventions 5.0.1 Oxford, UK: The Cochrane Collaboration; 2008; Chapter 9.

[18] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[19] Arand A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull 1999;47:15–7.

[20] Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.

[21] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[22] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[23] Herndon DN, Stein MD, Rutan TC, et al. Failure of TPN supplementa-tion to improve liver function, immunity, and mortality in thermally injured patients. J Trauma 1987;27:195–204.

[24] Dunham CM, Frankenfield D, Belzberg H, et al. Gut failure–predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? J Trauma 1994;37:30–4.

[25] Bauer P, Charpentier C, Bouchet C, et al. Parenteral with enteral nutrition in the critically ill. Intensive Care Med 2000;26:893–900.

[26] Huang YC, Yen CE, Cheng CH, et al. Nutritional status of mechanically ventilated critically ill patients: comparison of different types of nutritional support. Clin Nutr 2000;19:101–7.

[27] Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506–17.

[28] 2012;Luo Y, Jia WC, Wang Z. A comparison of effects between early enteral combined with parenteral nutrition versus early enteral nutrition in treating patients suffering from chronic obstructive pulmonary disease with acute exacerbation undergoing mechanical ventilation [in Chinese]. 24:436–8.

[29] Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381:385–93.

[30] Fan M, Wang Q, Fang W, et al. Early enteral combined with parenteral nutrition treatment for severe traumatic brain injury: effects on immune function, nutritional status and outcomes. Chin Med Sci J 2016;31: 213–20.

[31] Wischmeyer PE, Hasselmann M, Kummerlen C, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. Crit Care 2017;21:142.

[32] Wu W, Zhong M, Zhu DM, et al. Effect of early full-calorie nutrition support following esophagectomy: a randomized controlled trial. JPEN J Parenter Enteral Nutr 2017;41:1146–54.

[33] Ridley EJ, Davies AR, Parke R, et al. Supplemental parenteral nutrition versus usual care in critically ill adults: a pilot randomized controlled study. Crit Care 2018;22:12.

[34] Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;374:1111–22.

[35] Wan X, Gao X, Tian F, et al. Early parenteral nutrition alone or accompanying enteral nutrition in critically ill patients: a systematic review and meta-analysis. Asia Pac J Clin Nutr 2015;24:227–33.

[36] Shi J, Wei L, Huang R, et al. Effect of combined parenteral and enteral nutrition versus enteral nutrition alone for critically ill patients: a systematic review and meta-analysis. Medicine (Baltimore) 2018;97: e11874.

[37] Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature 2011;469:323–35.

[38] Saitoh T, Akira S. Regulation of innate immune responses by autophagy-related proteins. J Cell Biol 2010;189:925–35.

[39] Vanhorebeek I, Gunst J, Derde S, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab 2011;96:E633–45.

[40] Larsen BM, Goonewardene LA, Joffe AR, et al. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. Clin Nutr 2012;31: 322–9.

[41] Larsen BM, Field CJ, Leong AY, et al. Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants. JPEN J Parenter Enteral Nutr 2015;39:171–9.

[42] Kyle UG, Pirlich M, Lochs H, et al. Increased length of hospital stay in underweight and overweight patients at hospital admission: a controlled population study. Clin Nutr 2005;24:133–42.