Int J Clin Exp Med 2019;12(5):4755-4763
www.ijcem.com /ISSN:1940-5901/IJCEM0084275

Original Article

Early versus delayed enteral nutrition in critically ill patients: a meta-analysis of randomized controlled trials

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Received August 14, 2018; Accepted January 11, 2019; Epub May 15, 2019; Published May 30, 2019

Abstract: Purpose: To evaluate the effect of early enteral nutrition on the outcome of critically ill patients. Methods: PubMed, EMBASE, Springer, and the Cochrane Library were searched. Randomized controlled trials (RCTs) conducted in critically ill patients that compared the early enteral nutrition (EEN), provided within 48 h of intensive care unit (ICU) admission or post-operation, to delayed enteral nutrition (DEN) were included. Results: A total of 1725 patients were included in the 17 RCTs, with 862 in the EEN group and 863 in the control group. Results from a pooled analysis of all the studies demonstrated that early enteral nutrition was associated with significant reductions in overall complications (RR=0.81, 95% CI: 0.70-0.93, P=0.002), in infectious complications (RR=0.68, 95% CI: 0.51-0.91, P=0.009), in pneumonia (RR=0.76, 95% CI: 0.60-0.97, P=0.03), and in length of hospital stay(LOS) (mean difference -1.61; 95% CI: -3.02-0.20; P=0.03), but no difference was found in mortality or multiple organ failure (MOF) (P. > 0.05). Publication bias was found to be significant for the infectious complications (Pr=0.024, P.=0.001). No significant publication bias was found with respect to the other outcomes (Pr or P. > 0.05). Conclusions: Although no significant difference was observed in the risk of mortality, EEN within 48 h can improve the clinical outcomes of critically ill patients compared to DEN.

Keywords: Early enteral nutrition, critically ill patients, meta-analysis, systematic review, randomized controlled trials

Introduction

Nutritional support is considered an essential component of the management of critically ill patients [1]. Several published guidelines recommend that enteral nutrition (EN) should be started within the first 24-48 h after intensive care unit (ICU) admission when patients cannot eat or have eating contraindications [2-4].

Based on several RCTs, a meta-analysis revealed that EN started within 24 hours into the ICU can effectively reduce the incidence of pneumonia [Odds ratio (OR)=0.31, 95% confidence interval (CI) 0.12-0.78, I^2=0%] and mortality (OR=0.34, CI 0.14-0.85, heterogeneity: P=0.80), but has no obvious effect on reducing multiple organ failure (OR=0.94, CI 0.40-2.23) [5]. Another meta-analysis showed that early enteral nutrition (EEN) in patients with digestive tract surgery improved the nutritional status, reduced the risk of postoperative complications, shortened the length of hospital stays, and facilitated digestive system functional recovery [6].

At present, there are several mechanisms to elucidate why early enteral nutrition can improve patient outcomes. Insufficient enteral feeding leads to gastrointestinal mucosal atrophy, bacterial overgrowth, increased intestinal permeability, depletion of the liver's antioxidant enzymes, and potential bacterial translocation. Gut-associated lymphoid tissue plays a key role in mucosal immunity during starvation. Enteral nutrition can improve enteric blood flow, prevent structural and functional alterations of the gut barrier, maintain mucosal integrity,

decrease enteric permeability, and improve local and systemic immune responsiveness. Furthermore, enteral nutrition support attenuates the metabolic response to stress, limits oxidative cellular injury, and favorably modulates the immune response [7].

However, recent clinical trials have challenged the recommendations of the widely accepted clinical practice guidelines. The PYTHON trial did not demonstrate the superiority of EEN, as compared with an oral diet after 72 h, in reducing the rate of infection or death in patients with acute pancreatitis at a high risk for complications. A meta-analysis of these studies failed to reveal an improvement in any clinical outcome in the patients receiving normal caloric nutrition compared with trophic or permissive underfeeding [8]. Researches in recent years discovered that starvation promotes autophagy and this may play a key role in promoting host defenses [9, 10]. Anorexia is an evolutionary preserved response that may be beneficial during the first 48-72 h of acute illness [11].

Therefore, this study aims to perform an updated systematic literature review and meta-analysis to evaluate the overall effect of the route of nutrition (EEN versus DEN) on clinical outcomes in adult critically ill patients.

Materials and methods

Search strategy

Relevant articles about EN published from January 1990 to July 2017 were searched in PubMed, EMBASE, Springer, and the Cochrane Library. The following Medical Subject Heading (MeSH) or key words: “early enteral nutrition”, “early feeding”, “delayed or late enteral nutrition”, “randomized controlled trials”, and “controlled clinical trials” were searched. The literature search was limited to articles written in English.

Study selection

Studies included in this meta-analysis had to meet the following criteria: 1) study design: randomized clinical trial; 2) patients: hospitalized adult postoperative, trauma, severe head injuries, burn, acute pancreatitis or ICU patients; 3) intervention: early (within 48 h of admission or post-operation) vs. late/delayed enteral nutrition; 4) trial outcomes: at least one of the following variables: mortality including ICU, hospital, 28-day mortality or other; the number of infections; pneumonia (aspiration or VAP); complications; multiple organ failure (MOF); length of hospital stay (LOS).

Data extraction

The following information was obtained from the included RCTs: the first author, year of publication, the starting time of EN, the object of study, the number of participants, the start time and route of EN administration, intervention of the control group, the number of deaths, the infections (such as wound infection, infected pancreatic necrosis, bacteremia, et al.), pneumonia, complications, MOF and LOS of both early the EN group and the control group.

Statistical analysis

Statistical analyses were performed using a random effects model with the risk ratio (RR) metric by the computer program Review Manager (Version5.3 for Windows, Cochrane Collaboration, Oxford, UK). Also, STATA (Version 14.0; STATA Corporation, College Station, TX, US) was used in the quantitative assessment of publication bias as supplement.

All trial data were combined to estimate the pooled risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous variables (mortality, overall complication, infections, pneumonia, MOF) and the overall weighted mean difference (WMD) with 95% confidence intervals for LOS. The RR values of < 1.0 represented an advantage for the early EN group compared with late EN group. The overall effect was considered to be significant at the 0.05 level. Between-study heterogeneity was measured with a chi-square-based Q test and I^2. $P < 0.1$ or $I^2 > 50\%$ indicate that the analysis was reprsentative of statistically significant heterogeneity.

The potential publication bias was evaluated and demonstrated by Begg’s test and the Egger’s test with STATA quantitatively. A Pr or *P* value of less than 0.05 was considered representative of statistically significant publication bias.

Results

A total of 460 articles were searched from PubMed, EMBASE Databases, Springer, and the Cochrane library. The searching and screen ing of eligible studies is summarized in a

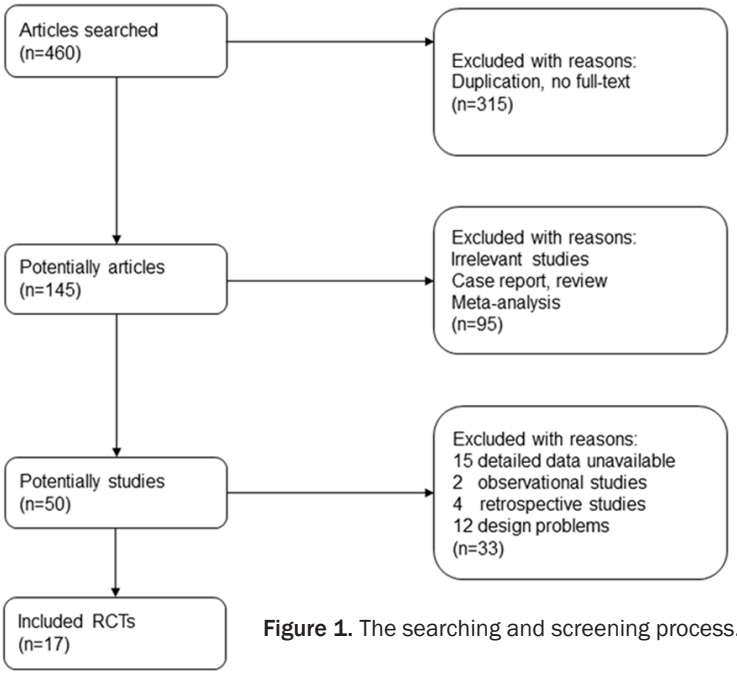

Figure 1. The searching and screening process.

PRISMA flow diagram in **Figure 1**. A total of 1725 patients were enrolled in the 17 RCTs, with 862 in the EEN group and 863 in the control group. Complete details of the included trials are presented in **Table 1** [12-28].

Effect of early versus delayed EN on mortality

The incidence of death was lower in the EEN group compared with the DEN group (9.21% VS 11.22%). However, there was no statistical significance between the two groups (RR=0.86, 95% CI: 0.60-1.23, P=0.42, heterogeneity I^2=0%; **Figure 2**).

Effect of early versus delayed EN on overall complications

A pooled analysis of 8 articles observing the complications revealed a significant reduction in the EEN group compared with DEN group (RR=0.81, 95% CI: 0.70-0.93, P=0.002; heterogeneity I^2=0%; **Figure 3**).

Effect of early versus delayed EN on infectious complications

A total of 12 studies reported on infectious complications. EEN compared to DEN was associated with a significant reduction in the incidence of infectious compli cations (RR=0.68, 95% CI: 0.51-0.91, P=0.009; **Figure 4**) and no heterogeneity was detected (P=0.23, I^2=22%).

The effect of early versus delayed EN on pneumonia

Information on the incidence of pneumonia was available for 11 of the 17 RCTs. The pooling of results (**Figure 5**) demonstrated a statistically significant reduction in pneu monia between the groups receiving EEN or DEN (RR=0.76, 95% CI: 0.60-0.97, P=0.03) with no evidence of heterogeneity (P=0.52, I^2=0%).

Effect of early versus delayed EN on MOF

Five trials reported the incidence of MOF. The pooling of results (**Figure 6**) failed to demonstrate any differences between the two groups (RR=0.82, CI: 0.59-1.14, P=0.23, no evidence of heterogeneity, I^2=0%).

Effect of early versus delayed EN on LOS

Eight articles observed the LOS (**Figure 7**). A significant reduction was detected when comparing EEN with DEN (mean difference -1.61; 95% CI: -3.02-0.20; P=0.03). However, there was significant heterogeneity between the studies (P < 0.00001, I^2=87%).

Risk of publication bias

The potential publication bias on the association of each clinical outcome and EEN was assessed and demonstrated by Begg's and Egger's test quantitatively. The publication bias was found to be significant for the infectious complications (Pr=0.024, P.=0.001). No significant publication bias was found with respect to the other outcomes (Pr or P. > 0.05; **Table 2**).

Discussion

This updated meta-analysis on the effect of EEN versus DEN on clinical outcomes included 17 randomized controlled trials with a total of 1725 randomized critically ill adult patients, and it revealed that EEN within 48 h of admission or post-operation reduced the statistically

Table 1. Complete details of included trials

Study	Patient	Early EN intervention	Control intervention	Reference
Chiarelli 1990	Burn patients	Immediately after hospitalization	48 h after hospitalization	[12]
Eyer 1993	Trauma	Immediately after admission to the ICU	72 h after admission to the ICU	[13]
Hasse 1995	Liver transplantation patients	12 h postoperatively	Eat orally once they passed flatus	[14]
Watters 1997	Major elective abdominal or thoracic surgery	Immediately postoperative	Until 6 postoperative days	[15]
Singh 1998	Nontraumatic Intestinal Perforation and Peritonitis	12 h postoperatively	After postoperative period	[16]
Pupelis 2001	Severe pancreatitis peritonitis	Within 12 h postoperatively	IV fluids until reintroduction of normal diet	[17]
Malhotra 2004	Gut perforations	Within 48 hours of admission	Receive intravenous alimentation for up to 7 days	[18]
Kaur 2005	Perforation peritonitis	Started on an EN regime 24 hours postoperatively	Eat orally once they passed flatus	[19]
Nguyen 2008	Critically ill patients	Within 24 h of admission	Until day 4 of admission	[20]
Minig 2009	Laparotomy	Within the first postoperative day	Until resolution of postoperative ileus	[21]
Dag 2011	Colorectal surgery	Oral feeding commencing approximately 12 hours after the operation with a fluid diet	Until the patient passed first flatus or stools	[22]
Chourdakis 2012	TBI	within 24-48 hours from admission to the ICU	> 48 hours but no later than 5 days after admission to the ICU	[23]
Vicic 2013	Burn patients	Within four hours after admission to the hospital.	Fed per os immediately after the first wound dressing.	[24]
Sun 2013	Acute Pancreatitis	The tube was placed within 24 h after admission, and EN was established from the next 24 h	Offered EN on the 8th day after admission, and a tube was placed on the 7th day	[25]
Bakker 2014	Acute Pancreatitis	EN was started at 20 ml per hour during the first 24 hours and was gradually increased	At 72 hours, the patients were given an oral diet. If not tolerated, it was offered again after 24 hours. If an oral diet still was not tolerated after 96 hours, nasoenteric feeding was started	[26]
Li 2015	Postoperative gastric cancer	Water was provided on the first day after surgery. If tolerated, EN were given on day 2 after surgery	After anal exhaust, the patient began to drink water orally.	[27]
Mahmoodzadeh 2015	GI tumor surgery	Initiated on the first postoperative day	Kept nil per os until the bowel sounds returned and resolution of ileus	[28]

EN: enteral nutrition, ICU: intensive care unit, TBI: traumatic brain injury, GI: gastrointestinal.

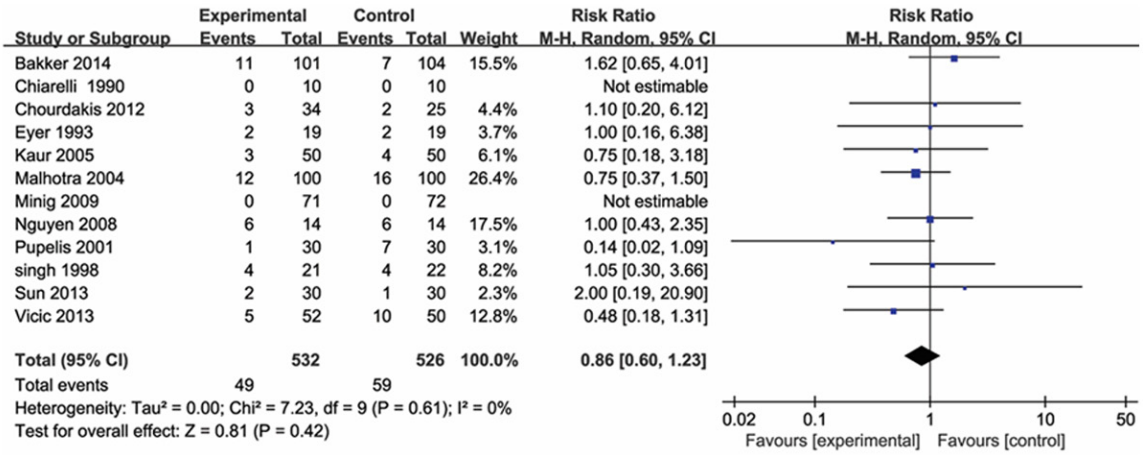

Figure 2. The effect of early versus delayed EN on mortality.

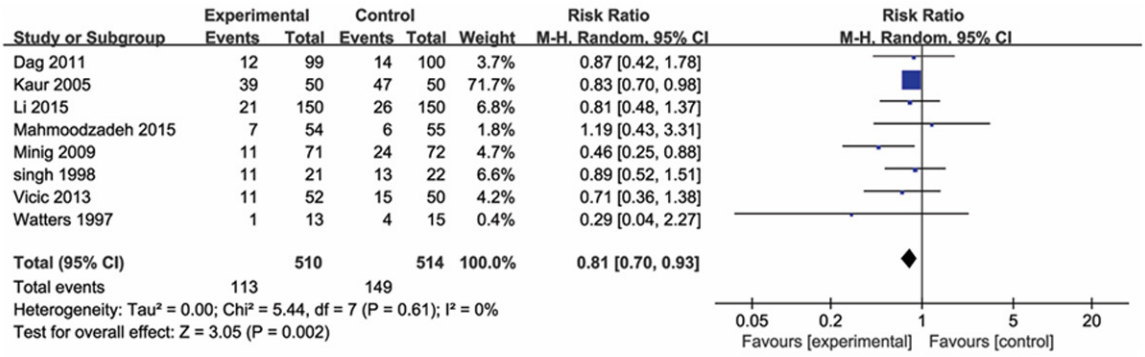

Figure 3. The effect of early versus delayed EN on overall complications.

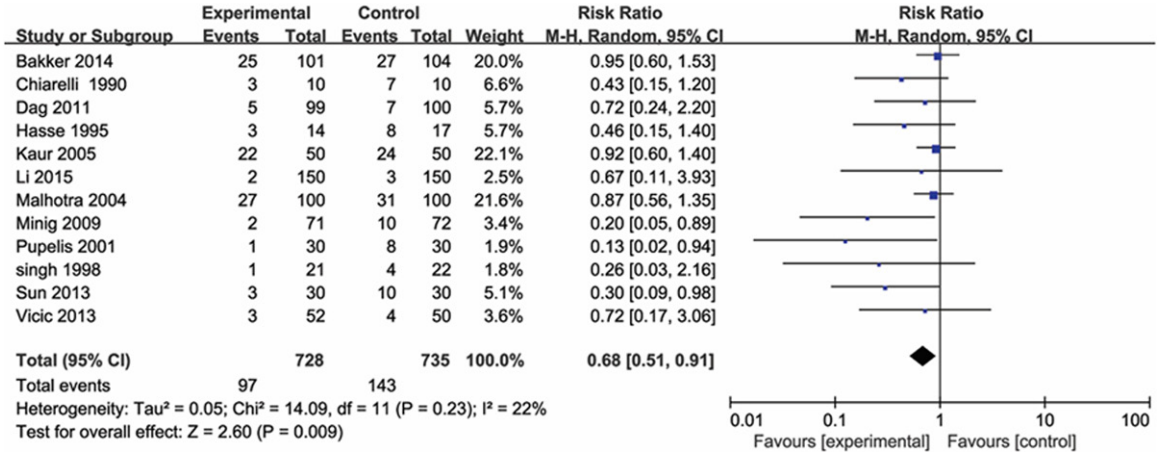

Figure 4. The effect of early versus delayed EN on infectious complications.

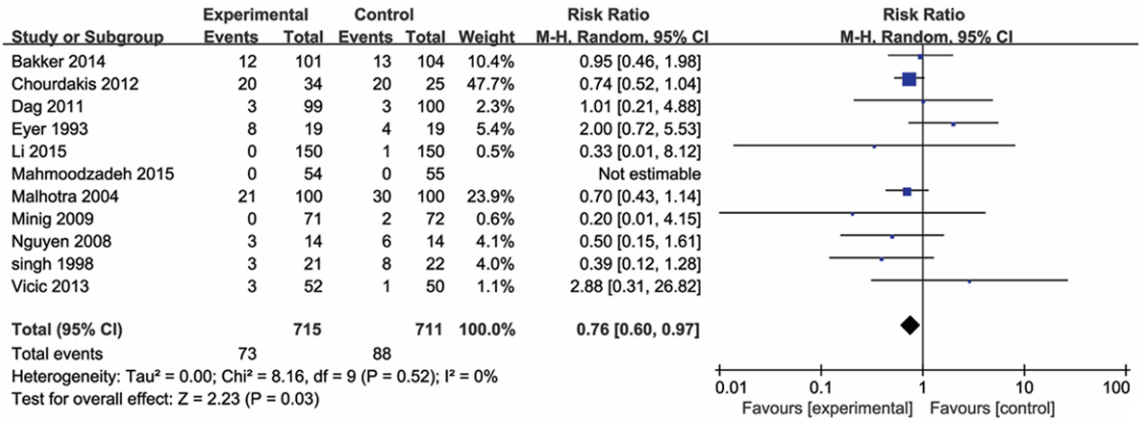

Figure 5. The effect of early versus delayed EN on pneumonia.

significant risk of overall complications, infection, pneumonia, and shortened the length of the hospital stay, compared to DEN. However, there was no benefit in reducing mortality or multiple organ failure between the two groups. Besides, we found no significant publication bias in all the outcomes except the infectious complications.

Three large previous meta-analysis compared the effect of EEN versus DEN on the clinical outcomes of critically ill adults [5, 29, 30].

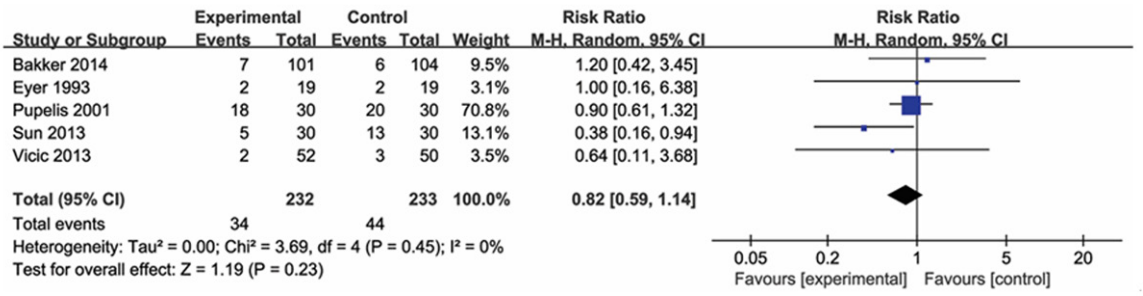

Figure 6. The effect of early versus delayed EN on MOF.

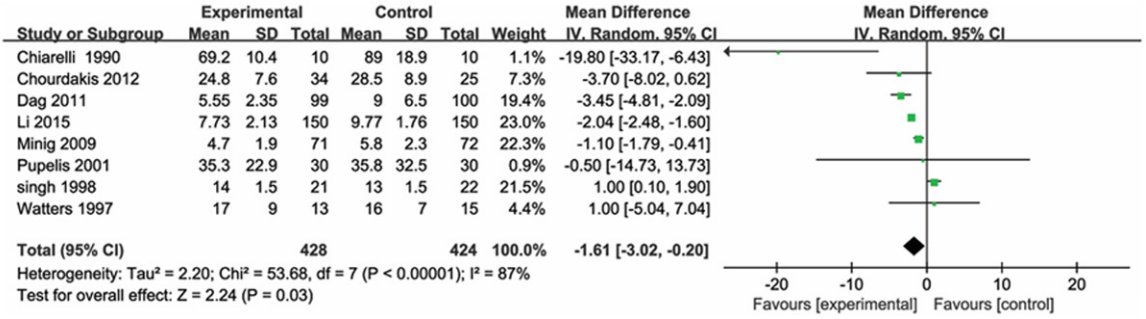

Figure 7. The effect of early versus delayed EN on LOS.

Table 2. Risk of publication bias

Clinical outcome	Begg's test (Pr.|z|=)	Egger's test (P.|t|=)
Mortality	0.858	0.781
Overall complications	0.711	0.378
Infectious complications	0.024	0.001
Pneumonia	0.592	0.921
MOF	0.806	0.703
LOS	0.386	0.106

However, the definition of "early" EN was different in these articles. The meta-analysis by Marik and Zaloga [29] included 15 RCTs and showed an infectious complications benefit of EEN, which was initiated within 36 h of admission to the hospital or within 36 h of surgery, compared to DEN (RR=0.45, 95% CI, 0.30-0.66, P=0.00006; heterogeneity, P=0.049); However, there were no significant differences in mortality (RR=0.74, 95% CI, 0.37-1.48; P=0.4; heterogeneity, P=0.92) between the two groups of patients. Unfortunately, a significant heterogeneity between the studies was found. In contrast to the above, a meta-analysis by Doig et al. [5] revealed that EEN, provided within 24 h of injury or intensive care unit admission, can significantly reduce the incidence of mortality (OR=0.34, 95% CI 0.14-0.85) and pneumonia (OR=0.31, 95% CI 0.12-0.78). Lastly, the third meta-analysis which was completed following the ESICM clinical practice guidelines demonstrated that EEN did not reduce mortality compared to delayed nutritional intake (RR 0.76; 95% CI 0.52-1.11; P=0.149; I^2=0%) but reduced the risk of infection compared to DEN (RR 0.64; 95% CI 0.46-0.90; P=0.010; I^2=25%) [30]. In our review, compared to DEN, EEN was associated with a significant reduction in the incidence of infectious complications but no benefit in mortality, which is the same as ESICM clinical practice guidelines. However, we also reviewed more clinical outcomes which are mentioned above (pneumonia, complications, LOS, MOF).

Nutritional support is an important part of the therapy of most critically ill patients. Early initiation via the enteral route has a significant effect on postoperative recovery in a wide variety of patients [31]. Up to now, the physiological mechanisms underlying the beneficial effect of EEN have yet to be fully elucidated. Factors that may play a role include the preservation of gut mass, the prevention of increased gut permeability to bacteria and other toxins, and the maintenance of the gut-associated lymphoid tissue

[32]. There is no consensus on the definition of "early". The term 'early' was defined as EN administration within postoperative day 3 [33]; however, 'early' has been more recently redefined as EN administration within 24-48 h after admission or surgery [5]. The ESICM Working Group defined "early" EN as EN started within 48 h independent of the type or amount, and this is also the definition used in this article.

Critically ill patients have a high risk of malnutrition [34]. Poor nutrition support at the early stage increases the risk of infections. Infection is one of the major factors contributing to poor outcomes. The gut houses the largest bacterial colonies, which are considered to be the 'motor' that drives the progression of multiple organ dysfunction syndrome (MODS) in critical illness [35]. The provision of early standard EN, resulting in the preservation of gut-associated lymphoid tissue, gut barrier function, the ability to detoxify LPS and reduce bacterial translocation [36-39], could explain a reduction in infections and pneumonia. In our review, EEN compared to DEN, there was a significant reduction in the incidence of infectious complications (RR=0.68, 95% CI: 0.51-0.91, P=0.009; heterogeneity I^2=22%) and pneumonia (RR=0.76, 95% CI: 0.60-0.97, P=0.03; heterogeneity I^2=0%).

Only five RCTs mentioned MOF, and they failed to find any differences the between two groups. The findings were consistent with the systematic review conducted by Doig et al. [5]. The studies included in our review may be insufficient, and more research is needed to confirm our conclusions. The reduction of infection and complications in the early EN group could result in a reduction of LOS and mortality. However, it was not exactly the same as what we found. There was a significant reduction LOS was detected between EEN and DEN, with a significant heterogeneity between studies (**Figure 7**). On the contrary, there was no difference between the two groups with regard to mortality (**Figure 2**), and the result was the same as the review in the ESICM clinical practice guidelines [34]. On the one hand, the mortality rate was associated with many factors. On the other hand, the extended definition of "early" to included trials that provided EN within 48 h may weaken the mortality benefit by the provision of EN within a 2 h window [5, 29].

We performed this updated meta-analysis to evaluate the effect of EEN on critically ill patients. Although there were few other studies on this issue, the criteria for patients included in our study are more comprehensive. In the current intensive care unit, there are numerous kinds of diseases and patients, including trauma, transplantation patients, burn patients, post-surgery, acute pancreatitis, traumatic brain injury, mechanical ventilation patients, severe infection, and so on. In order to minimize selection bias, all these diseases mentioned above were included in this analysis. The other strengths of our meta-analysis are the enrolled patient number and no obvious evidence of publication bias.

There are several limitations in our study. Firstly, the RCTs included in our meta-analysis were small and of poor quality. There is only one multicenter randomized controlled trial among all the included trials. Secondly, clinically heterogeneity exists in patient groups enrolled into the included trials. The EN formula used, the nutritional initial velocity, the nutritional goals, and the DEN groups also differ between trials. Thirdly, we did not conduct a subgroup analysis for different diseases. Lastly, the publication bias was found to be significant for the infectious complications (**Table 2**).

Conclusions

This study showed that EEN within 48 h of admission is associated with a reduced risk of complications, infection, pneumonia, and length of stay compared to DEN. However, no significant difference was observed in the risk of mortality, and multiple organ failure between the two groups. If there are no obvious enteral nutrition contraindications, EN therapy should be initiated as early as possible.

Disclosure of conflict of interest

None.

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