Original Article

Early parenteral nutrition comparing to enteral nutrition cannot reduce 28-day mortality in critically ill patients: a retrospective comparative cohort study based on the MIMIC-IV database

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Background: Enteral nutrition (EN) is recommended as the first choice by guidelines for critical ill patients. But the timing of safe and effective delivery of parenteral nutrition (PN) is unclear and the results of previous studies are controversial. There is insufficient evidence for the use of early PN, so we designed this cohort study to compared the clinical outcomes of critical ill patients who received early PN with those who did not.

Methods: This retrospective study conducted using the Medical Information Mart for Intensive Care (MIMIC)-IV database. Patients who received nutrition therapy within 3 days of ICU admission were included and we categorized them as patients who received any kind of PN (PN group) or only enteral nutrition (EN group). Confounding factors were adjusted by propensity-score matching (PSM). The primary outcome was the 28-day mortality rate, and secondary outcomes included length of stay (LOS) in the hospital and ICU, hospital infection, and mechanical ventilation time.

Results: A total of 5,019 patients (PN group, 357; EN group, 4,662) were included in the analyses. The 28-day mortality rates showed no significant intergroup difference (EN, 22.3% *vs.* PN, 20.2%; P=0.378). The PN group showed a shorter median ICU LOS (EN, 8.14 *vs.* PN, 6.89 days, P=0.00955), and a longer median hospital LOS (PN, 21.55 *vs.* EN, 15.1 days, P<0.001). After PSM, each group included 355 patients, with no significant intergroup difference in the 28-day mortality rate (EN, 18.9% *vs.* PN, 20.3%; P=0.705). The PN group still showed a longer hospital LOS (median LOS: PN, 21.45 *vs.* EN, 14.81 days, P<0.001), but the other outcomes showed no differences.

Conclusions: PN within 3 days of ICU admission did not reduce the 28-day mortality rate and could extend hospital LOS. This study supports further fundamental and clinical research to ascertain the effect of PN for ICU patients.

Keywords: Early parenteral nutrition; enteral nutrition; critical illness; Medical Information Mart for Intensive Care (MIMIC)-IV database

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Introduction

Critical illnesses, stress, and surgery all promote a catabolic state and negative nitrogen balance, which imposes additional strain on the body's nutritional needs. Studies have confirmed an association between caloric and/or protein deficits and increased mortality rates (1,2). Owing to their life-threatening and sometimes unconscious condition, most patients in intensive care units (ICUs) are unable to maintain a healthy diet. Any critically ill patient who spends more than 48 h in the ICU should be considered at risk of malnutrition (3), which is independently associated with worse clinical outcomes (4). Nutritional support, which aims to improve survival, limit the loss of lean body mass, and improve functional outcomes, is an essential component of critical care.

Despite significant advances in our knowledge of metabolic changes during critical illnesses, nutritional support in the ICU remains a complex task (5), so there is controversy regarding the timing of initiation, the targeted amount of macronutrients, and route of delivery. Enteral nutrition (EN) is cheap, physiological, and associated with fewer complications. It has been advocated as a means of reducing mucosal atrophy and increasing intestinal permeability, thereby reducing the incidence of gut translocation and septic complications. The enteral route is the mainstay of nutritional support in critical care but is frequently associated with gastrointestinal intolerance and underfeeding (6).

Highlight box

Key findings

- Addition of PN within 3 days of ICU admission did not improve the 28-day mortality rate and could extend hospital LOS. This study supports further fundamental and clinical research to ascertain the effect of PN on ICU patients.

What is known and what is new?

- Critical illnesses, stress, and surgery, which promote a catabolic state and negative nitrogen balance, impose additional strain on the body's nutritional needs.
- The present study aimed to assess the role of early PN by retrospectively analyzing data from ICU patients receiving nutritional support therapy.

What is the implication, and what should change now?

- We included patients who received any kind of PN within 3 days of ICU admission in the early PN group. Patients who received EN only in the first 3 days were included in the control group.

Total parenteral nutrition (PN) was popular in the 1970s and 80s, when it was used indiscriminately to counteract the metabolic problems associated with various illnesses. However, large randomized controlled trials (RCTs) in critically ill patients found no difference in mortality rates between PN and EN (7,8). Those studies provided new insights into the practical use of nutritional support therapies.

Some studies support that PN, with close monitoring to avoid overfeeding and hyperglycemia, is beneficial (9,10). A systematic review showed that the supplemental PN patients had shorter ICU stay and lower mortality rates than those on total PN (11). Current international guidelines recommend the enteral route for ICU patients without contraindications to EN (3,12,13). Complications related to PN have been an important topic in the guidelines. The timing of safe and effective delivery of PN is unclear. In a recent published RCT, early postoperative supplemental PN proved to be associated with reduced nosocomial infections and seemed a favorable strategy for patients with high nutritional risk and poor tolerance to EN (14). Owing to the limitations in our understanding of diseases and the complexity of the metabolic response to critical illness, further research is needed to answer emerging clinical questions in this regard.

The PN groups in many RCTs did not receive EN, which is not in line with the clinical reality. Moreover, there is no uniform definition of early PN. We believe that these are important factors that can cause biases in the results. Therefore, in the present study we aimed to assess the role of early PN by retrospectively analyzing data from ICU patients receiving nutritional support therapy. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6408/rc).

Methods

Study design and oversight

This retrospective study used a large critical care database, the Medical Information Mart for Intensive Care IV (MIMIC-IV) (15). The MIMIC-IV database is an updated version of the MIMIC-III and currently contains comprehensive and high-quality data of patients admitted to ICUs at the Beth Israel Deaconess Medical Center between 2008 and 2019. One author (BZ) obtained access to the database and was responsible for data extraction. The

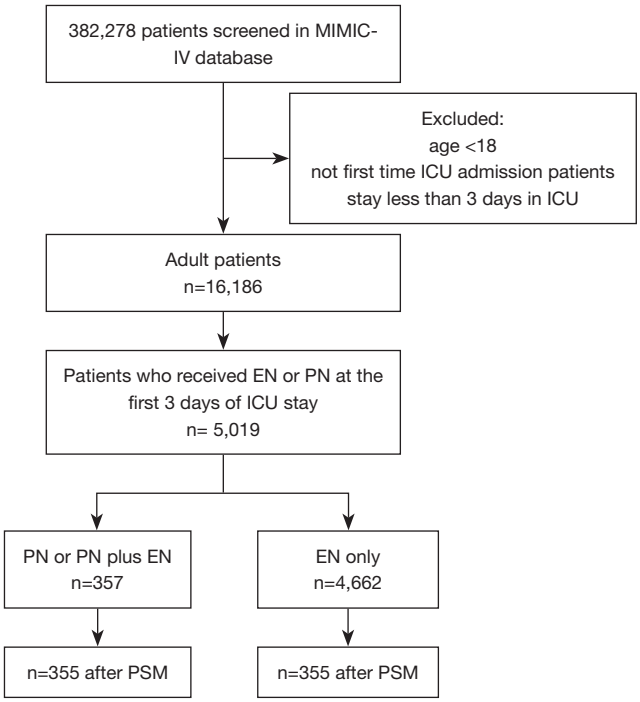

Figure 1 Flowchart of patient selection for the study. EN, enteral nutrition; ICU, intensive care unit; PN, parenteral nutrition; PSM, propensity-score matching.

study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Study population

The inclusion criteria were as follows: first admission to the ICU, over 18 years of age, and a medication/solution category of EN or PN during the first 3 days of ICU stay. The exclusion criteria were as follows: death within 3 days of ICU admission. The PN group was defined as patients who received PN or PN plus EN within 3 days of ICU admission, while the patients in the EN group received EN only.

The data were extracted using Structured Query Language. Because these underlying diseases are closely related to the nutrition status of the patient and the route of nutrition therapy. We extracted data on comorbidities such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes, paraplegia, renal disease, malignant cancer, severe liver disease, metastatic solid tumor, AIDS and dialysis status. Organ failure scores and life support measures are important aspect of the severity of the disease. So the data of ventilation use, vasopressor use and organ failure score were extracted or calculated. The following data were recorded: age, sex, weight, comorbidities, vital signs, test results on the first day, use of vasopressors, renal replacement therapy, mechanical ventilation, first-day Sequential Organ Failure Assessment (SOFA) score, first-day maximum Glasgow Coma Scale (GCS) score, length of ICU stay, length of hospital stay, and 28-day death. Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are expressed as percentages.

Primary and secondary outcomes

The primary outcome was 28-day death and the secondary outcomes included length of stay (LOS) in the hospital and ICU, hospital infection, and mechanical ventilation time.

Statistical analysis

Baseline characteristics are presented as mean (SD) and number (percentage) for continuous and categorical variables, respectively. We used the *t*-test, Chi-square (χ^2) test, or Wilcoxon rank-sum test to compare the patient characteristics between two groups as appropriate. LOS is presented as the median and was compared using the Mann-Whitney U test for nonparametric continuous variables. To further consider the robustness of the correction, we applied 1:1 nearest propensity-score matching (PSM) to balance the baseline characteristics between the two groups. In the PSM model, we matched individuals based on baseline comorbidities and life support measures with a caliper of 0.2 and outcomes were compared on the basis of the matched data. All analyses were performed using R software (version 4.0.1). The threshold of $P<0.05$ (two-sided) was considered statistically significant.

Results

A total of 5,019 patients were included in the analysis and of them, 357 received PN or PN+EN within the first 3 days of ICU stay, and 4,662 received EN only (*Figure 1*). The two groups showed no differences in age, sex, weight, vasopressor use, dialysis status, maximum lactate level, or first-day SOFA score (*Table 1*). The PN group showed a greater incidence of peptic ulcer disease (6.4% *vs.* 2.4%,

Table 1 Patients' characteristics and baseline values

Baseline characteristics	EN (n=4,662)	PN (n=357)	P value
Male sex, n (%)	2,625 (56.3)	183 (51.3)	0.073
Age, years, mean (SD)	62.76 (16.90)	62.06 (15.94)	0.45
Weight, kg, mean (SD)	83.00 (25.93)	79.40 (21.65)	0.012
SOFA score, mean (SD)	8.37 (3.93)	8.52 (4.81)	0.493
Charlson comorbidity index, mean (SD)	5.59 (3.01)	5.62 (3.07)	0.886
Myocardial infarction, n (%)	682 (14.6)	41 (11.5)	0.121
Congestive heart failure, n (%)	1,234 (26.5)	81 (22.7)	0.133
Peripheral vascular disease, n (%)	438 (9.4)	43 (12.0)	0.122
Cerebrovascular disease, n (%)	1,343 (28.8)	26 (7.3)	<0.001
Dementia, n (%)	209 (4.5)	7 (2.0)	0.033
Chronic pulmonary disease, n (%)	1,223 (26.2)	86 (24.1)	0.408
Rheumatic disease, n (%)	149 (3.2)	16 (4.5)	0.246
Peptic ulcer disease, n (%)	112 (2.4)	23 (6.4)	<0.001
Mild liver disease, n (%)	685 (14.7)	75 (21.0)	0.002
Diabetes without cc, n (%)	1,105 (23.7)	63 (17.6)	0.011
Diabetes with cc, n (%)	369 (7.9)	13 (3.6)	0.005
Paraplegia, n (%)	688 (14.8)	9 (2.5)	<0.001
Renal disease, n (%)	842 (18.1)	54 (15.1)	0.186
Malignant cancer, n (%)	556 (11.9)	93 (26.1)	<0.001
Severe liver disease, n (%)	333 (7.1)	34 (9.5)	0.119
Metastatic solid tumor, n (%)	222 (4.8)	44 (12.3)	<0.001
AIDS, n (%)	35 (0.8)	4 (1.1)	0.65
Sepsis, n (%)	4,065 (87.2)	299 (83.8)	0.075
Dialysis present, n (%)	290 (6.2)	23 (6.4)	0.957
Max. lactate, mmol/L, mean (SD)	2.99 (2.93)	3.04 (2.71)	0.772
Min. PaO_2/FiO_2 ratio, mean (SD)	203.66 (123.39)	181.94 (99.73)	0.006
Ventilation use, n (%)	3,210 (68.9)	195 (54.6)	<0.001
Vasopressor use, n (%)	1,558 (33.4)	115 (32.2)	0.683
Min. GCS, mean (SD)	9.02 (4.00)	10.06 (4.21)	<0.001

EN, enteral nutrition alone; PN, parenteral nutrition; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; cc, complication or comorbidity; AIDS, acquired immunodeficiency syndrome; Max, maximum; Min, minimum; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale.

P<0.001), malignant cancer (26.1% *vs.* 11.9%, P<0.001), and metastatic solid tumors (12.3% *vs.* 4.8%, P<0.001) than the EN group, which could have led to greater PN requirements. The EN group showed a greater incidence of cerebrovascular disease (28.8% *vs.* 7.3%, P<0.001) and paraplegia (14.8% *vs.* 2.5%, P<0.001) than the PN group. The PN group also showed a lower PaO_2/FiO_2 ratio (181.94 *vs.* 203.66, P=0.006) and less use of mechanical ventilation (54.6% *vs.* 68.9%, P<0.001).

The overall 28-day mortality rate was 22.2%, with no difference between groups (EN, 22.3% *vs.* PN, 20.2%, P=0.378). The PN group showed a shorter LOS in the ICU (median LOS: EN, 8.14 *vs.* PN, 6.89 days, P=0.00955), but a longer LOS in the hospital (median LOS: PN, 21.55 *vs.*

Table 2 Invasive ventilation time and hospital infections before propensity-score matching

Invasive ventilation time and hospital infections	Before matching		
	EN	PN	P value
Invasive ventilation time, h, mean (SD)	20.73 (18.01)	23.82 (22.89)	0.225
Hospital infections, n (%)	510 (10.9)	19 (5.3)	0.001

EN, enteral nutrition alone; PN, parenteral nutrition; SD, standard deviation.

EN 15.1 days, P<0.001). The duration of invasive mechanical ventilation was similar between the two groups (mean ventilation period: PN, 23.82 h *vs.* EN, 20.73 h, P=0.2258). The EN group showed a higher rate of hospital infections than the PN group (10.9% *vs.* 5.3%, P=0.001) (*Table 2*).

The characteristics of the 710 patients were balanced between the two groups after PSM (*Table 3*). The two groups showed no difference in the 28-day mortality rate (EN, 18.9% *vs.* PN, 20.3%; P=0.705; odds ratio =0.91, 95% CI: 0.63–1.33) (*Figure 2*). After PSM, the two groups showed no difference in the ICU LOS (median LOS: PN, 6.89 *vs.* EN, 7.01 days, P=0.7322). The PN group still had a longer hospital LOS (median LOS: PN, 21.45 *vs.* EN, 14.81 days, P<0.001) (*Figure 3*). The invasive mechanical ventilation time was still similar in the two groups after matching (mean ventilation period: PN, 23.79 h *vs.* EN, 19.9 h; P=0.2024). The matched data showed no difference in the hospital infection rate (PN, 5.1% *vs.* EN 7.6%, P=0.218) (*Table 3*).

Discussion

Optimal nutritional support is the cornerstone of critical care for patients admitted to the ICU, but the controversy surrounding nutritional therapy in the ICU remains unresolved. Our study showed that the addition of PN within 3 days of ICU admission did not improve the 28-day mortality rate and could extend hospital LOS, which is a new perspective on PN in ICU practice. A recent study that collected data from 28 different countries from 2007 to 2018 showed a lack of consensus between European and non-European countries regarding the timing, preferred route of administration, and total energy targets of nutritional treatment strategies for ICU patients over the past decade (16). Some authors believe that supplemental PN plays a pivotal role in the achievement of adequate feeding in critically ill patients with intolerance to EN, while others believe that PN may lead to prolonged dependency on intensive care, increased incidence of new infections, and muscle weakness (17,18).

The value of early EN initiation is supported by physiological data. During the ICU stay, EN maintains gut integrity, supports the diversity of the microbiome, sustains gut-associated lymphoid tissue and mucosa-associated lymphoid tissue at distant sites, and stimulates T2 anti-inflammatory lymphocytes and T-regulatory cells (19). Current evidence suggests that early EN support is well tolerated in patients with shock and may be associated with improved clinical outcomes (20).

Several multicenter RCTs have investigated the timing of PN in critically ill patients. The definitions of early PN in these studies varied, and the results were slightly different. The lack of a uniform definition of early PN may be partly responsible for the confusion in the results. The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study was conducted in patients whose caloric targets could not be met by EN alone (21). In that study, early PN was initiated on day 3 and late PN on day 8. The EPaNIC study showed no significant difference in deaths, but late PN was associated with faster recovery and fewer complications than early PN. Another early PN trial conducted in critically ill adult patients with short-term relative contraindications to EN found no significant differences in mortality or infection rates (8). In that trial, early PN was initiated 44 min after enrollment. The early PN strategy resulted in significantly fewer days of invasive ventilation, but not significantly shorter ICU or hospital LOS. The results of the Early versus Late PN in the Pediatric Intensive Care Unit (PEPaNIC) trial were published in 2016 (22). The early PN group in the PEPaNIC study received PN within 24 h after admission. Withholding PN for 1 week resulted in fewer new infections, a shorter duration of dependency on intensive care, and a shorter hospital stay, but the mortality rate was similar between groups. Based on those previous studies, we defined PN within 3 days as early PN and consistent with the previous findings, our study found no change in mortality rate after adding PN in the first 3 days in the ICU.

Another finding of our study was the absence of a difference in the hospital infection rates between the groups. A meta-analysis comparing the routes of nutrient delivery showed no difference in mortality rates but revealed a significant reduction in infectious complications when

Table 3 Patients' characteristics and baseline values after PSM

Characteristics after matching	EN (n=355)	PN (n=355)	P value
Male sex, n (%)	171 (48.2)	183 (51.5)	0.409
Age, years, mean (SD)	61.48 (16.29)	62.03 (15.97)	0.65
Weight, kg, mean (SD)	80.51 (27.07)	79.46 (21.70)	0.571
SOFA score, mean (SD)	7.43 (4.18)	7.75 (4.45)	0.309
Charlson comorbidity index, mean (SD)	5.41 (3.12)	5.59 (3.06)	0.452
Myocardial infarction, n (%)	33 (9.3)	41 (11.5)	0.39
Congestive heart failure, n (%)	87 (24.5)	81 (22.8)	0.659
Peripheral vascular disease, n (%)	33 (9.3)	42 (11.8)	0.329
Cerebrovascular disease, n (%)	25 (7.0)	26 (7.3)	1
Dementia, n (%)	8 (2.3)	7 (2.0)	1
Chronic pulmonary disease, n (%)	95 (26.8)	86 (24.2)	0.491
Rheumatic disease, n (%)	19 (5.4)	16 (4.5)	0.729
Peptic ulcer disease, n (%)	21 (5.9)	23 (6.5)	0.876
Mild liver disease, n (%)	63 (17.7)	74 (20.8)	0.342
Diabetes without cc, n (%)	58 (16.3)	63 (17.7)	0.69
Diabetes with cc, n (%)	12 (3.4)	13 (3.7)	1
Paraplegia, n (%)	12 (3.4)	9 (2.5)	0.658
Renal disease, n (%)	47 (13.2)	54 (15.2)	0.519
Malignant cancer, n (%)	93 (26.2)	91 (25.6)	0.932
Severe liver disease, n (%)	27 (7.6)	34 (9.6)	0.422
Metastatic solid tumor, n (%)	40 (11.3)	42 (11.8)	0.907
AIDS, n (%)	3 (0.8)	4 (1.1)	1
Sepsis, n (%)	284 (80.0)	298 (83.9)	0.204
Dialysis present, n (%)	25 (7.0)	23 (6.5)	0.881
Max. lactate, mmol/L, mean (SD)	2.86 (2.89)	3.04 (2.71)	0.45
Min. PaO_2/FiO_2 ratio, mean (SD)	194.42 (118.79)	182.47 (99.56)	0.221
Ventilation use, n (%)	189 (53.2)	195 (54.9)	0.707
Vasopressor use, n (%)	113 (31.8)	115 (32.4)	0.936
Min. GCS, mean (SD)	9.89 (3.94)	10.07 (4.20)	0.555
Invasive ventilation time, h, mean (SD)	19.90 (15.97)	23.79 (22.93)	0.202
Hospital infection, n (%)	27 (7.6)	18 (5.1)	0.218

PSM, propensity-score matching; EN, enteral nutrition alone; PN, parenteral nutrition; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; cc, complication or comorbidity; AIDS, acquired immunodeficiency syndrome; Max, maximum; Min, minimum; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale.

exclusive EN was used (23). However, this benefit was most likely due to reduced intake of macronutrients during EN and a publication bias. Three other meta-analyses found that the association between death and calorie intake did not depend on the route of nutrient delivery (EN *vs.* EN + PN) (24-26). PN was harmful only when it was associated

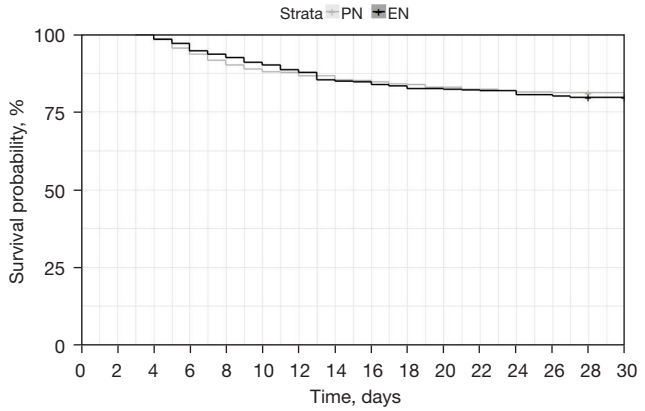

Figure 2 Survival curves of the EN and PN groups after propensity-score matching. EN, enteral nutrition; PN, parenteral nutrition.

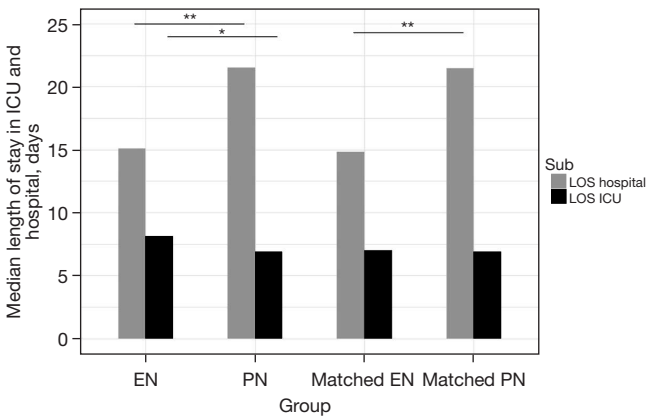

Figure 3 Median length of stay in the ICU and hospital in the EN and PN groups. *P<0.01, **P<0.001. EN, enteral nutrition; LOS, length of stay; ICU, intensive care unit; PN, parenteral nutrition.

with increased calorie intake.

Evidence-based guidelines on nutrition in critically ill patients have changed over time with the emergence of more studies. However, well-designed RCTs have failed to demonstrate the benefit of EN over PN with respect to death. In the CALORIES trial, 2400 critically ill adult patients who could be fed by either route were randomized to receive early EN or early PN. Caloric intake was similar in both groups. The primary endpoint (death at 30 days) was unaffected, and more vomiting caused by early EN was observed (7). In the NUTRIREA-2 trial, Reignier *et al.* compared early isocaloric EN with early isocaloric PN with a normocaloric target in ventilated adults with shock (27). They failed to find superiority in the mortality rates associated with early EN over early PN, and their data indicated an increased risk of gastrointestinal complications with early EN.

In our study, the PN group had a longer hospital LOS, which remained significant after PSM. The LOS in the ICU and mechanical ventilation time in the two groups were similar. Early PN during critical illness can evoke a phenotype of autophagy deficiency in the liver and skeletal muscle (28), which may be associated with ICU-acquired weakness and lung injury and may be related to a longer rehabilitation course (29,30). Hyperglycemia and hypoglycemia are common in critically ill patients receiving PN. Another study showed that increased glycemic variability is associated with increased duration of mechanical ventilation and ICU LOS (31).

Despite the lack of solid evidence that early EN could reduce the mortality rate, the clinical guidelines of the European Society of Intensive Care Medicine still recommend early EN rather than PN in the ICU because of the belief that EN reduces infectious complications (32). The Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) recommend that nutritional support therapy in the form of early EN should be initiated within 24–48 h, and the use of supplemental PN should be considered after 7 to 10 days (13). The German Society for Nutritional Medicine (DGEM) considers that the enteral route of nutrient delivery should still be preferred in the acute phase, largely because of its economic but not clinical superiority. They recommended supplemental PN for all patients in whom exclusive EN cannot guarantee sufficient calorie and protein intake according to the phase of the disease and individual metabolic tolerance (12). Nevertheless, the enthusiasm for EN has ignored the fact that a parenteral supply of substrates can be beneficial for intestinal health: PN supports the renewal rate of intestinal cells, increases the rate of intestinal protein synthesis, and reduces the apoptosis rate (33).

The primary limitation of our study is the lack of individual calorie intake data. Due to missing data and the presence of incorrect data, the calculated calorie/body weight measurements were unreliable. Therefore, we could not compare the nutrition targets achieved by the two groups. The high heterogeneity of diseases in critically ill patients is another important factor that may cause bias.

With regard to the adverse effects of early PN, malnutrition may be an important problem in most regions of the world. A retrospective observational study in the ICU setting in eight Latin American countries showed

that malnutrition was highly prevalent, and caloric intake failed to meet energy delivery targets in 40% of critically ill adults receiving nutrition therapy (34). Supplemental PN administration was associated with improved energy and protein delivery; however, PN use was low. Collectively, these findings indicate an opportunity for more effective utilization of supplemental PN in critically ill adults who fail to receive adequate nutrition from EN alone. Opposing enteral or parenteral feeding is no longer rational in critical care settings. Thus, a single guideline may not be suitable for different ICU patients, and personalized prescriptions that meet the nutritional targets of critically ill patients by combining EN and PN may be a better solution.

Conclusions

In comparison with EN alone, the addition of PN within 3 days of ICU admission did not improve the 28-day mortality rate. Moreover, administration of PN could lead to a longer LOS in the hospital, but not in the ICU. More fundamental and clinical research is needed to ascertain the effect of early PN on critical ill patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6408/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6408/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

References

1. Alberda C, Gramlich L, Jones N, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35:1728-37.
2. Nicolo M, Heyland DK, Chittams J, et al. Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study. JPEN J Parenter Enteral Nutr 2016;40:45-51.
3. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48-79.
4. Lew CCH, Yandell R, Fraser RJL, et al. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review [Formula: see text]. JPEN J Parenter Enteral Nutr 2017;41:744-58.
5. Al-Dorzi HM, Arabi YM. Nutrition support for critically ill patients. JPEN J Parenter Enteral Nutr 2021;45:47-59.
6. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med 2014;370:1227-36.
7. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med 2014;371:1673-84.
8. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309:2130-8.
9. Weijs PJ, Stapel SN, de Groot SD, et al. Optimal protein and energy nutrition decreases mortality in mechanically ventilated, critically ill patients: a prospective observational cohort study. JPEN J Parenter Enteral Nutr 2012;36:60-8.
10. Weijs PJ, Looijaard WG, Beishuizen A, et al. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. Crit Care 2014;18:701.
11. Sharma SK, Rani R, Thakur K. Effect of Early Versus Delayed Parenteral Nutrition on the Health Outcomes of

Critically Ill Adults: A Systematic Review. J Crit Care Med (Targu Mures) 2021;7:160-9.
12. Elke G, Hartl WH, Kreymann KG, et al. Clinical Nutrition in Critical Care Medicine - Guideline of the German Society for Nutritional Medicine (DGEM). Clin Nutr ESPEN 2019;33:220-75.
13. Taylor BE, McClave SA, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med 2016;44:390-438.
14. Gao X, Liu Y, Zhang L, et al. Effect of Early vs Late Supplemental Parenteral Nutrition in Patients Undergoing Abdominal Surgery: A Randomized Clinical Trial. JAMA Surg 2022;157:384-93.
15. Alistair Johnson, Lucas Bulgarelli, Tom Pollard, Steven Horng, Leo Anthony Celi, Roger Mark. MIMIC-IV (version 1.0) Available online: https://physionet.org/content/mimiciv/1.0/2021
16. Veraar C, Geilen J, Fischer A, et al. Timing of parenteral nutrition in ICU patients: A transatlantic controversy. Clin Nutr ESPEN 2021;46:532-8.
17. Oshima T, Heidegger CP, Pichard C. Supplemental Parenteral Nutrition Is the Key to Prevent Energy Deficits in Critically Ill Patients. Nutr Clin Pract 2016;31:432-7.
18. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013;1:621-9.
19. Arabi YM, Casaer MP, Chapman M, et al. The intensive care medicine research agenda in nutrition and metabolism. Intensive Care Med 2017;43:1239-56.
20. Patel JJ, Rice T, Heyland DK. Safety and Outcomes of Early Enteral Nutrition in Circulatory Shock. JPEN J Parenter Enteral Nutr 2020;44:779-84.
21. 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.
22. 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.
23. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20:117.
24. Chelkeba L, Mojtahedzadeh M, Mekonnen Z. Effect of Calories Delivered on Clinical Outcomes in Critically Ill Patients: Systemic Review and Meta-analysis. Indian J Crit Care Med 2017;21:376-90.
25. Parikh HG, Miller A, Chapman M, et al. Calorie delivery and clinical outcomes in the critically ill: a systematic review and meta-analysis. Crit Care Resusc 2016;18:17-24.
26. Ridley EJ, Davies AR, Hodgson CL, et al. Delivery of full predicted energy from nutrition and the effect on mortality in critically ill adults: A systematic review and meta-analysis of randomised controlled trials. Clin Nutr 2018;37:1913-25.
27. Reignier J, Boisramé-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018;391:133-43.
28. Derde S, Vanhorebeek I, Güiza F, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology 2012;153:2267-76.
29. Yang J, Sun H, Tian F, et al. Autophagy suppression plays a role in parenteral nutrition-associated lung injury. Clin Nutr 2021;40:560-70.
30. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care 2015;19:274.
31. Doola R, Greer RM, Hurford R, et al. Glycaemic variability and its association with enteral and parenteral nutrition in critically ill ventilated patients. Clin Nutr 2019;38:1707-12.
32. Reintam Blaser A, Starkopf J, Alhazzani W, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med 2017;43:380-98.
33. Hartl WH, Alpers DH. The trophic effects of substrate, insulin, and the route of administration on protein synthesis and the preservation of small bowel mucosal mass in large mammals. Clin Nutr 2011;30:20-7.
34. Vallejo KP, Martínez CM, Matos Adames AA, et al. Current clinical nutrition practices in critically ill patients in Latin America: a multinational observational study. Crit Care 2017;21:227.

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