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Original article

Effect of Early Versus Late Parenteral Nutrition on the Outcome of Critically Ill Patients

Basem M.Aglan[a], Sally S.Mohamed[b], Hossam E.Mahmoud, Eslam A.Shaboob[c]

[a]Department of Cardiothoracic Surgery, Faculty of Medicine Benha University, Egypt.

[b]Department of Critical Care Medicine and Intensive Care Unit, Faculty of Medicine, Cairo University, Egypt.

[c]Department of Anaesthesia and Intensive Care, Faculty of Medicine Benha University, Egypt.

Corresponding to: Hossam E.Mahmoud, Anaesthesia and Intensive Care, Faculty of Medicine Benha University, Egypt.

Email:

hossameldingamal8@gmail.com

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Abstract

Background: Serious illness can lead to malnutrition, which worsens infections, makes mechanical ventilation last longer, slows recovery, and raises the risk of death **This study aimed to** in critically ill adult patients, compare the intensive care outcomes based on the initiation of parenteral nutrition (PN) within 7 days versus after 7 days of inadequate nutrient intake. **Methods:** This multicenter parallel group randomized controlled trial included 100 included patients who were recruited from the critical care units at Benha University hospital and Cairo Fatemic Hospital within six months. Patients divided into two equal groups: Group A (n=50): Patients were assigned for early PN. Group B (n=50): Patients were assigned for late PN. **Results**: The outcome was significantly different between both groups, showing significantly higher improved cases among patients who received early PN compared to those who received late PN (P=0.015). **Conclusion:** Adults in critical illness fared better when PN was started within 7 days as opposed to after 7 days of intensive care, but both groups had higher scores on the acute physiology and chronic health evaluation surveys.

Keywords: Late Parenteral Nutrition; Early Parenteral Nutrition; Critically Ill Patients.

Introduction

Patients with critical illnesses are at increased risk for malnutrition, which can worsen infections, lengthen the time they need mechanical ventilation, slow their recovery, and even increase their mortality [(1)]. Enteral nutrition (EN) is generally regarded as the most viable approach; however, it is not always feasible. Additionally, the effectiveness of early initiation or delayed initiation of parenteral nutrition (PN) remains uncertain, as algorithms for PN exhibit significant heterogeneity [(2)].

The optimal time to initiate parenteral nutrition (PN) for critically ill individuals in the absence of endotracheal insufficiency remains a topic of debate. The guidelines have been issued by the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine. These guidelines stipulate that patients who do not have a high risk of malnutrition, as demonstrated by tests such as the Nutrition Risk in Critically Ill (NUTRIC) score of 5 or NRS 2002 [Nutrition Risk Screening] ⩽3, should wait seven days before commencing PN. In instances where early EN is not feasible for patients who are at a high risk of malnutrition or have a high nutrition score (e.g., NRS 2002–20 or NUTRIC score–5) [(3)].

For patients who are unable to receive enteral nutrition (EN) and are not anticipated to receive regular feeding within three days, the European Society for Clinical Nutrition and Metabolism recommends initiating parenteral nutrition (PN) within twenty-four to forty-eight hours of admission to the intensive care unit(ICU) [(4)].

The objective of this investigation was to contrast the outcomes of intensive care in critically ill adult patients who were initiated on PN within seven days against those who were initiated on PN after seven days of inadequate nutrient intake.

Patients and methods

This multicenter parallel group randomized controlled trial included 100 included patients who were recruited from the critical care units at Benha University hospital and Cairo Fatemic hospital within six months started form the approval of the protocol.

From 6-11-2022 to 6-5-2023

The patients were given informed written permission. Every patient had a secret code number and explained the goal of the research. The study commenced following approval from Cairo Fatemic Hospital, Benha University Hospital, Faculty of Medicine, and Research Ethics Committee.

Inclusion criteria were Patients admitted to the ICU who were 18 years old or older and had a Nutrition Risk

Score (NRS) of 3 or higher (on a scale from 1 to 7, where 3 signifies nutritional risk).

Exclusion criteria were individuals with a body mass index (BMI) below 17, ability to tolerate oral nutrition or a predetermined nutritional regimen, diabetic coma, patients with short bowel syndrome, those without central venous access, patients who received concurrent EN, and so on.

Grouping: Patients divided into two equal groups: **Group A (n=50):** Patients were assigned for early PN. **Group B (n=50):** Patients were assigned for late PN.

All studied cases were subjected to the following: Full history taking, including [personal history (personal data as age, BMI and daily caloric need), The patient's current and past medical histories, as well as any risk factors such as hypertension, diabetes mellitus, chronic liver disease, chronic kidney disease, organ dysfunction, BMI, obesity, and age all play a role in the nutrition outcomes.

Full clinical examination: General examination including (heart rate, temperature, blood pressure, and other vital signs), chest, cardiac, and both the lower and upper extremities. Lab tests that are part of a routine evaluation include electrolytes (sodium, potassium, calcium, magnesium, and phosphate levels), coagulation profile (prothrombin time, partial thromboplastin time, and international normalized ratio), tests for renal and liver function (urea and creatinine), and a full blood count (regular blood glucose level, urine analysis, and random blood glucose level).

Half of the patients were assigned to early PN, and the other half were assigned to late PN. ICU and hospital mortality were recorded.

Nutrition risk screening

The lack of malnutrition was indicated by an NRS score of 0, while a score of 3 or higher indicated a high risk of malnutrition. The screening tool has been proven effective in multiple randomized control trials that have been published before. If a patient's NRS 2002 score was high but they weren't critically ill, it could indicate a poor prognosis. Critical care settings can make it challenging to assess dietary intake and weight loss. Critically sick patients with an APACHE II score greater than 10 are at high risk, which is one of the key limitations of the NRS 2002 score [(5)].

Early treatment group patients received an intravenous 20% glucose solution; on day one of their ICU stay, they were to consume 400 kcal of total calories per day; on day two, 800 kcal. Starting PN (OliClinomel or Clinimix, Baxter) on day 3 to reach 100% of the calorie aim was performed if the clinicians felt the patient could manage enough oral feeding or EN that day.

The daily PN amount was determined by subtracting the total energy intake from the caloric goal from the amount that EN effectively delivered. The protein energy component was factored into the calorie goal calculations, which were based on the corrected ideal body weight, age, and sex.

Every patient received instructions to eat no more than 2,880 kcal daily. When EN reached 80% of the projected calorie target or when the patient was judged capable of starting oral nutrition, PN either dropped off or was eliminated. PN was started again when food intake from enteral feedings or orally dropped below half of the advised calorie intake. Patients in the group that started treatment later were given a 5% glucose solution in the same volume as the patients in the group that started treatment earlier, considering the volume of EN that was given to make sure they were hydrated enough. If EN was still inadequate after seven days in the ICU on day eight PN began to approach the caloric target.

Unless medically contraindicated, all patients unable to eat by day two received EN (mostly Osmolite, Abbott), while under a semi-recumbent posture. All patients were instructed to use prokinetic agents and to feed through the duodenum in addition to increasing the EN infusion rate twice daily per the standing EN orders.

Each patient's daily enteral and PN dosage was determined using a patient data management system (MetaVision, iMDsoft) in accordance with the protocol. The attending ward physicians had discretion over nutritional management following ICU discharge. Controlling blood glucose levels was achieved by adjusting the continuous insulin infusion to a range of 80 to 110 mg/dL (4.4 to 6.1 mmol/L) [6, 7].

Chemical analysis was carried out on a blood gas analyzer (Radiometer ABL 715 and 725, Radiometer Medical) every 1 to 4 hours to monitor arterial blood glucose levels, and adjustments were made as needed. The ICU that took part in the study all adhered to the standards for weaning patients off ventilators. Two senior ICU doctors and the referring specialist reached a consensus on end-of-life care when it was determined that further treatment was futile.

Evaluation of the outcomes including ICU stays, hospital stays, nutrition score, acquisition of new morbidities or infections and BMI.

Outcome:

Vital status, incidence of complications and hypoglycemia, mortality rates in the ICU and the hospital, survival rates up to 90 days after ICU and hospital discharge, and proportion of patients still alive at 8 days or less after ICU discharge were all included as safety end points. Significant adverse events occurred if hypoglycemia continued despite the administration of parenteral

glucose during the intervention window. The total number of days spent in the ICU, including those of patients who did not survive, plus the time it took to be discharged, was the main end point. The number of patients who needed a tracheostomy, how long antibiotics were taken, how many days until the last mechanical ventilatory support was withdrawn, how much inflammation was measured by the highest plasma C-reactive protein level, and where the infection was located (airways, lungs, bloodstream, urinary tract, or wounds) were all secondary end points.

Approval code: MS 6-11-2022

Statistical analysis

The statistical study was conducted using SPSS v28, a program created and maintained by IBM in Armonk, New York, USA. To compare the two datasets for quantitative factors like means and standard deviations, we utilized an unpaired Student's T-test. To analyze the qualitative variables, either Fisher's exact test or a chi-square test was deployed. The data were expressed as frequencies (%) or percentages (%) when appropriate. As soon as the two-tailed P value fell below 0.05, we knew that our results had shown statistical significance.

Results

BMI was significantly higher in patients who received early parenteral nutrition compared to patients who received late parenteral nutrition (P=0.042), regarding age and sex there were an in significant difference between both groups. between patients who received early parenteral nutrition and patients who received early parenteral nutrition and those who received late parenteral nutrition in terms of sepsis (caused by: community-acquired pneumonia, chest infections, UTIs, dialysis catheter infections, septicemia, endocarditis, HAP, meningitis, peritonitis, spontaneous bacterial peritonitis, septicemia, gangrenous loops, severe acute respiratory distress syndrome (ARDS), skin infections, septicemia, surgical site infections, external fistulas, and surgical wound infections) were an insignificantly different. Patients who were given parenteral nutrition early had a significantly lower risk of organ failure compared to those who were given it later (P=0.009). Different types of cancer were significantly more common in patients who got parenteral nutrition early during treatment compared to those who got it later (P=0.029). Early parenteral nutrition patients had a considerably higher APACHE score than late parenteral nutrition patients (P=0.008), but there was no statistically significant difference in the nutritional risk screening score between the two classifications **Table 1**

Table 2 shows that PN indications were significantly different between patients who received early parenteral nutrition compared to those who received late parenteral nutrition regarding tolerance (P=0.001).

When comparing tolerance between patients who got parenteral nutrition early and those who got it late, there was no statistically significant difference (P=0.044). There was a statistically significant difference in the incidence of new morbidities between patients who received parenteral nutrition early in the day and those who received it later in the day. Patients who got parenteral nutrition early had a significantly lower risk of developing a new infection than those who got it late (P=0.043). When comparing patients who got MV tracheostomy early vs those who got it late, there was no significant difference. **Table 3**

The results were significantly different between the two groups, with patients who received early parenteral nutrition demonstrating significantly higher rates than those who received late parenteral nutrition (P=0.015). **Table 4**

Table 1: Baseline characteristics, comorbidities, sepsis studied patients**.**

			Total (n=100)	Early (n=50)	Late (n=50)	P value
Baseline characteristics	**age**	**Mean ±SD**	53.8 ± 14.99	55.2 ± 15.43	52.4 ± 14.57	0.367
		range	22-81	22 - 72	22 - 81	
	sex	**male**	68 (68%)	36 (72%)	32 (64%)	0.391
		female	32 (32%)	14 (28%)	18 (36%)	
	BMI	**Mean ±SD**	27.7 ± 5.82	28.8 ± 5.76	26.5 ± 5.69	**0.042***
		range	20-41	20 - 38	20 - 41	
Comorbidities		**HTN**	60 (60%)	30 (60%)	38 (76%)	0.087
		DM	52 (52%)	24 (48%)	29 (58%)	0.265
	sepsis		68 (68%)	34 (68%)	33 (66%)	0.832
Organ failure		**cancer colon**	2 (2%)	0 (0%)	2 (4%)	**0.009***
		IO	2 (2%)	0 (0%)	2 (4%)	
		cirrhotic liver	12 (12%)	4 (8%)	8 (16%)	
		CKD	14 (14%)	8 (16%)	6 (12%)	
		COPD	2 (2%)	0 (0%)	2 (4%)	
		ESRD RHD	2 (2%)	0 (0%)	2 (4%)	
		Extensive MVO	2 (2%)	2 (4%)	0 (0%)	
		HF	6 (6%)	6 (12%)	0 (0%)	
		AF	4 (4%)	4 (8%)	0 (0%)	
		PVD	4 (4%)	0 (0%)	4 (8%)	
		respiratory failure	2 (2%)	2 (4%)	0 (0%)	
		DCL	4 (4%)	2 (4%)	2 (4%)	
		RTA	4 (4%)	2 (4%)	2 (4%)	
Cancer		**colon cancer**	8 (8%)	2 (4%)	6 (12%)	**0.029***
		colorectal cancer	2 (2%)	2 (4%)	0 (0%)	
		oesophageal cancer	2 (2%)	0 (0%)	2 (4%)	
		cancer head pancreas	2 (2%)	2 (4%)	0 (0%)	
		lung cancer	4 (4%)	0 (0%)	4 (8%)	
		prostatic cancer	3 (3%)	2 (4%)	0 (0%)	
		stomach cancer	2 (2%)	0 (0%)	2 (4%)	
		cholangiocarcinoma	4 (4%)	2 (4%)	2 (4%)	
		HCC	8 (8%)	4 (8%)	4 (8%)	
		pyloric mass	2 (2%)	2 (4%)	0 (0%)	
		perirectal cystic lesion & enlarged LNs	2 (2%)	0 (0%)	2 (4%)	
APACHE score		**Mean ±SD**	41.6 ± 10.7	44.4 ± 10.72	38.8 ± 10.03	**0.008***
		range	20-60	30 - 60	20 - 60	
Nutritional risk screening score		**Mean ±SD**	4.9 ± 0.65	4.96 ± 0.6	4.92 ± 0.7	0.760
		range	4-6	4 - 6	4 - 6	

BMI: body mass index, HTN: hypertension, DM: diabetes mellitus. IO: intestinal obstruction, CKD: chronic kidney disease, COPD: chronic obstructive disease, ESRD: End-Stage Renal Disease, MVO: microvascular obstruction, HF: heart failure, AF: atrial fibrillation, PVD: Peripheral vascular disease, RTA: renal tubular acidosis, HCC: hepatocellular carcinoma, LNs: lymph nodes, APACHE: acute physiology and chronic health evaluation, *: statistically significant as p value <0.05.

Table 2: PN indications of the studied patients

		Total (n=100)	Early (n=50)	Late (n=50)
PN indications	**abdominal compartment syndrome**	6 (6%)	4 (8%)	2 (4%)
	septic shock	46 (46%)	22 (44%)	24 (48%)
	burn	4 (4%)	4 (8%)	0 (0%)
	neurogenic shock	4 (4%)	4 (8%)	0 (0%)
	spinal shock	2 (2%)	0 (0%)	2 (4%)
	hypovolemic shock	4 (4%)	2 (4%)	2 (4%)
	contraindication for EN	6 (6%)	4 (8%)	2 (4%)
	insufficient EN	6 (6%)	0 (0%)	6 (12%)
	unavailable post pyloric EN	2 (2%)	2 (4%)	0 (0%)
	eclampsia	2 (2%)	0 (0%)	2 (4%)
	status epilepticus	2 (2%)	0 (0%)	2 (4%)
	risk aspiration	6 (6%)	4 (8%)	2 (4%)
	gastric outlet obstruction	2 (2%)	2 (4%)	0 (0%)
	GI bleeding	8 (8%)	4 (8%)	4 (8%)
	high flow ileostomy	2 (2%)	0 (0%)	2 (4%)
	high output colostomy	6 (6%)	2 (4%)	4 (8%)
	short bowel syndrome	2 (2%)	0 (0%)	2 (4%)
	ultrashort bowel	6 (6%)	6 (12%)	0 (0%)
	internal fistula	2 (2%)	2 (4%)	0 (0%)
	intestinal ischemia	2 (2%)	2 (4%)	0 (0%)
	malnutrition	2 (2%)	0 (0%)	2 (4%)
	peritonitis	2 (2%)	4 (8%)	0 (0%)
	perforated viscus	2 (2%)	2 (4%)	0 (0%)
	respiratory failure	4 (4%)	2 (4%)	2 (4%)
	high dose vasopressors	2 (2%)	0 (0%)	2 (4%)

PN: parenteral nutrition, EN: enteral nutrition, MV: mechanical ventilation, GI: gastrointestinal.

Table 3: tolerance, incidence of new morbidities, MV tracheostomy of the studied patients and the studied groups regarding the parenteral nutrition

		Total (n=100)	Early (n=50)	Late (n=50)	P value
Tolerance	**Overfeeding**	12 (12%)	28 (56%)	20 (40%)	**0.044***
	Tolerance	48 (48%)	14 (28%)	26 (52%)	
	Underfeeding	40 (40%)	8 (16%)	4 (8%)	
New morbidities		82 (82%)	2 (4%)	4 (8%)	0.602
Incidence of new infection	**Chest infection**	6 (6%)	2 (4%)	4 (8%)	**0.043***
	HAP	12 (12%)	8 (16%)	4 (8%)	
	CVL infection	10 (10%)	6 (12%)	4 (8%)	
	Endocarditis	2 (2%)	2 (4%)	0 (0%)	
	Infected colostomy	2 (2%)	0 (0%)	2 (4%)	
	Multiple lung abscesses	2 (2%)	0 (0%)	2 (4%)	
	Septicaemia	2 (2%)	0 (0%)	2 (4%)	
	ARDS	2 (2%)	0 (0%)	2 (4%)	
	Skin infection	2 (2%)	2 (4%)	0 (0%)	
	Surgical site infection	4 (4%)	0 (0%)	4 (8%)	
	UTI	2 (2%)	0 (0%)	2 (4%)	
	VAP	14 (14%)	6 (12%)	8 (16%)	
MV tracheostomy	**Yes**	66 (66%)	30 (60%)	34 (68%)	0.306
	ETT to secure airway	2 (2%)	2 (4%)	0 (0%)	

HAP: hospital-acquired pneumonia, CVL: central venous line, ARDS: acute respiratory distress syndrome, UTI: urinary tract infection, VAP: ventilator-associated pneumonia, MV: mechanical ventilation, ETT: endotracheal tube. *: statistically significant as p value <0.05.

Table 4: Outcome of the studied groups regarding the parenteral nutrition

		Total (n=100)	Early (n=50)	Late (n=50)	P value
Outcome	**Died**	42 (42%)	16 (32%)	28 (56%)	**0.015***
	Improved	58 (58%)	34 (68%)	22 (44%)	

*: statistically significant as P value <0.05

Discussion

Usually, patients admitted into the ICU have life-threatening diseases. This results in major catabolic stress, which over time can cause notable loss of muscle mass and compromised function. It is generally believed that the catabolic response can be mitigated by ensuring sufficient nutrition with vital nutrients. However, it is still a complex challenge for ICU doctors to determine when, how much, and what kind of nutrition support is necessary [(3)].

Earlier retrospective studies linked energy or protein deficits to unfavorable outcomes, including longer durations on mechanical ventilation, more frequent infectious complications, and lengthier stays in the ICU and the hospital. However, nutritional therapy reduces this risk [(8)].

The patients whose ages were taken into consideration had a mean of 53.8 ± 14.99 years and a range of 22 to 81 years. There were 68 men and 32 women, or 68% and 32%, respectively. The patients' body mass indexes ranged from 20 to 41 Kg/m2, with a mean of 27.7 5.82 Kg/m2, in the study. Sixty patients, or 60%, had hypertension, and fifty-two patients, or 52%, had diabetes. Septomyxis affected 68 out of the 102 patients analyzed.

Similarly, They enrolled patients on day 3 of admission to the ICU and determined that age was 61 ±16 years and BMI (kg/m²) of 25.4 ± 3.9 in

patients who take EN plus supplemental PN [(9)].

Also, (10) found that the participants' ages ranged from 18 to 40 years, with an average age of 36.34±2.77. There were 315 men and 237 women who took part.

In this study the APACHE score of the studied patients ranged from 20 to 60 with a mean of 41.6 ± 10.7.

[(10)] found that a sum of 228 patients out of 552 patients admitted for medical or surgical reasons who stayed in the ICU for more than 24 h had the APACHE score from 20 to 40.

However, [(9)] showed that APACHE II score was 22 ± 7 in patients who take EN plus supplemental PN.

In the present study, 12 (12%) patients had overfeeding, 48 (48%) patients had tolerance, and 40 (40%) patients had underfeeding. The Nutritional risk screening score ranged from 4 to 6 with a mean of 4.9 ± 0.65.

The PN indications among the studied patients included septic shock which was the most common cause in 46 (46%) patients, followed by GI bleeding in 8 (8%) patients. The incidence of new morbidities was reported in 82 (82%) patients. The incidence rate of new

infection was reported in 56 (56%) patients.

Our study shows that 66 (66%) patients required mechanical ventilation (MV) tracheostomy and 2 (2%) patients required endotracheal tube (ETT) to secure airway. Regarding the outcome, 42 (42%) patients had been died, while 58 (58%) patients had been improved.

Similarly, [11] investigate the connection between acute care unit nutrition practices, the implementation of early nutrition support (<48 hours), and patient mortality on day 28. The findings revealed that 1206 patients were assessed in total. Invasive mechanical breathing was necessary for up to 81.2% of patients.

No statistically significant difference was found between the two groups with respect to age, sex, or the accompanying comorbidities such as hypertension (HTN), diabetes mellitus (DM), or sepsis. However, patients whose PN was administered early had a higher BMI than those whose PN was administered late.

There was a significant difference between patients who received early PN and those who received late PN regarding the organ failure and cancer type.

Similarly, [11] Describe the nutritional policies used in the (ICU), look at the relationship between early nutrition support (within the first 48 hours) and patient mortality on day 28, and observe that early nutrition was more frequently prescribed when multiple organ failure was present.

With no appreciable difference between the two groups regarding the nutritional risk screening score, the APACHE score was noticeably higher in patients who received early PN than late PN.

While there was no statistically significant difference in tolerance or overfeeding between the groups according to the timing of PN administration, there was a difference between the groups according to how long it took to administer PN.

Compared to those who got early PN, the late PN group had an insignificantly greater frequency of new morbidities. Between patients who had early PN and those who received late PN, the incidence of new infections was significantly different.

This was in line with [12], Infections in the ICU were lower in the group that started treatment later compared to the one that started treatment earlier.

Additionally, [13] discovered that although 18.5% of patients in the early PN group experienced the development of a new infection, only 10.7% of patients in the late PN group did it. Our results were like theirs, but they did not include 1440 children with severe illnesses, unlike us.

Also, another study by [14] discovered a decrease in new infections in the Late PN group when compared to the Early PN group.

There was an insignificant difference between patients who received early PN compared to those who received late PN regarding MV tracheostomy.

In contrary, [12] found that the percentage of patients needing mechanical ventilation for more than two days decreased by 9.7 percent in the group that started treatment later (P=0.006).

The outcome was significantly different between both groups, showing significantly higher improved cases than dead cases among patients who received early PN compared to those who received late PN.

In line with most of the previous findings, [15], There was no correlation between early PN initiation and better clinical outcomes compared to late EN or PN, although their findings did indicate that early PN initiation may improve calorie and protein provision.

However, [12] They found that starting PN early might make it easier to provide calories and protein, but it didn't lead to better clinical outcomes than starting EN or PN later.

In disagreement, [11] stated that early nutrition was significantly associated with mortality.

In difference, a single-center, retrospective study by [16] they demonstrated there was in statistically significant difference in in-hospital mortality between the groups, but they also came to the conclusion that the time it took to start PN had no bearing on this metric.

In contrary, [13] showed that mortality was similar in the two groups. However, they included 1440 critically ill children which differ from us.

While, a previous systematic review by [17] stated that while definitive conclusions cannot be drawn due to the varied study designs and quality assessments, it is safe to presume that there are no clinically significant advantages to administering PN early in critically ill adults compared to administering it late in terms of end point morbidity or mortality.

In disagreement with our study results, a recent study by [18] found no significant difference in two-year mortality or physical functioning between the two groups, even after accounting for missing data on physical functioning. Similarly, in terms of physical functioning and 2-year mortality, Late-PN did not affect any nutritional risk subgroup. One possible explanation for this discrepancy is that their follow-up period is two years shorter than ours.

The limitation of the study was a relatively small sample size compared to previous studies which may contribute to insignificant results and lack of assessment the association between risk factors and outcome of ICU.

Conclusion

From the current study results, initiation of PN within 7 days led to more improved cases compared to PN after 7 days intensive care for critically ill adult patients, but with higher APACHE score. While both early and late PN showed comparable clinical outcome, thus further studies with larger sample size are recommended.

Therefore, despite the comparable results between both groups, we recommend utilizing early PN over late early PN for critically ill adult patients in ICU, conducting same study aim and methodology on larger sample size and

longer follow up period and assessment the association between risk factors and outcome of ICU will be insightful.

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