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Original article

Early supplemental parenteral nutrition is associated with reduced mortality in critically ill surgical patients with high nutritional risk

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SUMMARY

Background & aims: Adequate nutritional provision is important for critically ill patients to improve clinical outcomes. Starting enteral nutrition (EN) as early as possible is recommended and preferred to parenteral nutrition (PN). However, patients who undergo emergency abdominal operations may have alterations in their intra-abdominal environment and gastrointestinal motility leading to limitation in starting an enteral diet. Therefore, our study was designed to evaluate the benefit of early supplemental PN to achieve adequate calorie and protein supply in critically ill patients undergoing surgery who are not eligible for early EN.

Methods: We reviewed the medical records of 317 patients who underwent emergency abdominal surgery for complicated intra-abdominal infection (cIAI) between January 2013 and December 2018. The nutritional data of the patients were collected for 7 days in maximum, starting on the day of intensive care unit (ICU) admission. The patients were divided by low or high malnutrition risk using the modified Nutrition Risk in Critically ill (mNUTRIC) score and body mass index. The low- and high-risk groups were subdivided into the following two categories: those who received PN within 48 h ("early") and those who did not ("usual"). Data regarding the baseline characteristics, initial severity of illness, morbidity, and mortality rates were also obtained. The average calorie and protein supply per day were calculated in these groups.

Results: Patients in all groups showed no significant differences in baseline characteristics, initial status, and infectious complications. In terms of outcomes, patients with low malnutrition risk had no significant difference in mortality. However, among patients with high malnutrition risk, the "Early" group had lower rates of 30-day mortality (7.6% vs. 26.7%, $p = 0.006$) and in-hospital mortality (13.6% vs. 28.9%, $p = 0.048$) than those of the "Usual" group. Kaplan–Meier survival curves for 30-day mortality in these groups also showed a statistically significant difference ($p = 0.001$). The caloric adequacy of the "Early" group and the "Usual" group were 0.88 ± 0.34 and 0.6 ± 0.29, respectively. Amounts of protein received were 0.94 ± 0.39 g/kg in the "Early" group and 0.47 ± 0.34 g/kg in the "Usual" group, respectively. There was no significant difference in infectious complications between both groups.

Conclusions: Mortality in patients with high malnutrition risk who received early PN supply within 48 h after emergency surgery for cIAI was lower than those who did not receive PN earlier. PN may be necessary to fulfill the caloric and protein requirements for critically ill patients who cannot achieve their nutritional requirements to the fullest with EN alone.

1. Introduction

Adequate nutritional provision is important for critically ill patients to improve clinical outcomes. Greater amount of nutritional intake during the first week in the intensive care unit (ICU) is

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associated with longer survival time and faster recovery [1]. Delivering early nutrition support therapy, primarily by the enteral route, is seen as a proactive therapeutic strategy that may reduce disease severity, diminish complications, decrease length of stay (LOS) in the ICU, and favorably impact patient outcomes [2,3]. Providing early enteral nutrition (EN) postoperatively in patients undergoing elective major abdominal surgery has also been proven to be safe and effective in improving gut oxygenation [4].

However, patients who undergo emergency abdominal operations may have alterations in their gastrointestinal (GI) anatomy as well as intra-abdominal environment and GI motility, causing limitations to enteral diet. According to the renowned critical care guidelines, starting parenteral nutrition (PN) in those with limitations to early EN is recommended with strong consensus [2]. Contrarily, several studies reported that the provision of early PN had no benefit on the survival rate in critically ill patients [5,6].

Yet the clinical conditions of critically ill patients are highly heterogeneous and their nutritional status also varies according to their conditions. In a study of critically ill patients with a high risk of malnutrition, receiving at least 800 kcal/day of nutrition reduced their mortality rate [7]. Furthermore, in a study of critically ill patients after GI surgery, patients with high nutrition risk had a better survival rate if they received adequate caloric or protein supply, either with EN or PN [8]. Therefore, supplemental PN may be beneficial in achieving adequate caloric and protein supply for critically ill patients with high nutritional risk, especially those who are not eligible for early EN.

This study investigated critically ill patients in a surgical ICU with high nutritional risk and compared the 30-day mortality between the patients who received supplementary PN within 48 h after surgery and those who did not.

2. Materials and methods

2.1. Study design and patients

A retrospective analysis was conducted on data prospectively collected from January 2013 to December 2018. A total of 1581 patients underwent emergency abdominal surgery during this period in the Department of Surgery in a tertiary medical center in South Korea. Of these, 1264 patients were excluded because they were not admitted through the emergency department (ED) or did not require postoperative intensive care. Finally, 317 patients who were admitted via the ED, needed postoperative intensive care, and were confirmed of having a complicated intra-abdominal infection (cIAI) in the operational field were included in this study. The patients were divided by nutritional risk using the modified Nutrition Risk in Critically ill (mNUTRIC) score and body mass index (BMI) [9,10]. Patients with a mNUTRIC score of $\geq$5 or BMI of <18.5 kg/m^2 were classified as being at high risk for malnutrition [11]. The low- and high-risk groups were subdivided into those who received PN within 48 h ("Early") or those who did not ("Usual") (Fig. 1).

2.2. Clinical and demographic data

Data regarding the patients' baseline characteristics, such as age, sex, body weight, height, BMI, number of comorbidities, diagnosis, location of the lesion, the modality of the surgery, and the existence of GI perforation were collected from their admission and operation notes through electronic medical records.

Data of indicators of initial severity of illness in the ED, including the variables for calculating the mNUTRIC score, were collected, in terms of Acute Physiology and Chronic Health Evaluation II (APACHE II), American Society of Anesthesiology (ASA) score, quick sequential organ failure assessment (qSOFA) score, full sequential organ failure assessment (SOFA) score, and systemic inflammatory response syndrome (SIRS).

Data reflecting clinical outcomes, such as hospital length of stay (HLOS), ICU length of stay (LOS), mechanical ventilation (MV) days, in-hospital mortality, and 30-day mortality were recorded, and the morbidity during their hospital stay, if occurred, were also obtained.

2.3. Caloric and protein intake data and calculation of adequacy

The nutritional data of the patients were collected for maximum 7 days, starting on the day of ICU admission. Daily requirements of calories and protein were calculated based on the patient's body weight multiplied by 25 kcal/kg/day; for patients on continuous renal replacement therapy, 30 kcal/kg/day was applied.

Daily input of supplied PN or EN was obtained in volumes (mL) from the ICU sheet. Based on the nutritional information provided by manufacturers of each PN or EN products, calories (kcal) and amount of protein (g) supplied per 1 mL were multiplied to the infused volume. Then, the average caloric and protein supply per day and their adequacy were calculated.

2.4. Statistical analysis

Data normality was tested using the Shapiro–Wilk test. Continuous variables, presented as means ± standard deviations or medians [interquartile range] depending on the data normality, were compared using Student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables, presented as frequency (%), were compared using the chi-square test or Fisher's exact test. Kaplan–Meier survival curves and log-rank tests were used to compare the 30-day mortality between the groups. Patient data with any missing variables were excluded from the analysis. The results were statistically significant at $P < 0.05$. Statistical analysis was performed using SPSS Statistics 25.0 (IBM Corp., Armonk, NY), SAS (version 9.4, SAS Inc., Cary, NC, USA), and R package (version 3.1.3, http://www.R-project.org).

3. Results

3.1. Baseline characteristics and initial severity of illness

A total of 317 patients received postoperative care in the surgical ICU after emergency GI surgery with cIAI. Among them, the nutritional risk of 111 patients was classified as high and accounted for 35.0% of the total number of patients. The high-risk patients showed no significant differences in baseline characteristics and initial status between the "Early" and "Usual" groups (Table 1, Table 2).

However, the low-risk patients showed several differences between the "Early" and "Usual" groups. The patients with low nutritional risk who received PN within 48 h were older (66.50 [56.00, 76.00] vs 63.00 [49.00, 73.00] years; $p = 0.031$) and had a higher Charlson Comorbidity Index (3.00 [2.00, 5.00] vs 3.00 [2.00, 4.00]; $p = 0.028$) than those in the "Usual group" (Supplementary Table 1).

The initial severity of illness of the enrolled patients was evaluated with APACHE II, ASA classification, qSOFA, full SOFA score, SIRS, initial systolic blood pressure, respiratory rate, mental status, and mNUTRIC score. In the high-risk group, the "Early" and "Usual" groups did not show a significant difference in the initial severity of illness (Table 2).

Furthermore, there were no significant differences in the initial severity of illness between the two groups under the low nutritional risk (Supplementary Table 2).

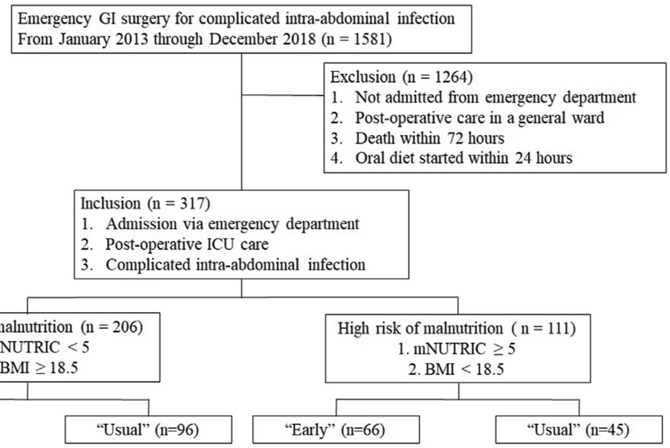

Fig. 1. Study population. GI, gastrointestinal; ICU, intensive care unit; mNUTRIC, modified Nutrition Risk in Critically ill; BMI, Body Mass Index.

Table 1
Baseline characteristics (high-risk group).

	Early (n = 66)	Usual (n = 45)	*p* value
Age, year	77.50 [62.75, 82.00]	76.00 [67.00, 80.00]	0.616[a]
Sex (M/F), n (%)	28 (42.4)/38 (57.6)	23 (51.1)/22 (48.9)	0.367
Body weight, kg	53.76 ± 11.09	56.48 ± 12.59	0.232
Height, cm	161.32 ± 8.10	161.87 ± 9.78	0.748
BMI, kg/m^2	20.63 ± 3.86	21.47 ± 4.13	0.278
Charlson Comorbidity Index, n	4.68 ± 2.17	4.40 ± 1.95	0.486
Comorbidity, n (%)			
Hypertension	38 (57.6)	30 (66.7)	0.334
CAOD	12 (18.2)	5 (11.1)	0.310
DM	20 (30.3)	16 (35.6)	0.562
CRF	3 (4.5)	5 (11.1)	0.379[b]
Malignancy	12 (18.2)	12 (26.6)	0.345
COPD	4 (6.1)	2 (4.4)	1.000[b]
LC	2 (3.0)	2 (4.4)	1.000[b]
Diagnosis, n (%)			0.206[b]
Mechanical	22 (33.3)	21 (46.7)	
Vascular	13 (19.7)	10 (22.2)	
Ulceration	25 (37.9)	9 (20.0)	
Infection	6 (9.1)	4 (8.9)	
Location, n (%)			0.053[b]
Stomach	19 (28.8)	7 (15.6)	
Duodenum	5 (7.6)	2 (4.4)	
Small bowel	26 (39.4)	13 (28.9)	
Large bowel	15 (22.7)	20 (44.4)	
Multifocal	1 (1.5)	3 (6.7)	
Perforation, n (%)	47 (71.2)	35 (77.8)	0.439
Laparoscopy/open, n (%)	15 (22.7)/51 (77.3)	5 (11.1)/40 (88.9)	0.138

M/F, male/female; BMI, body mass index; CAOD, coronary artery occlusive disease; DM, diabetes mellitus; CRF, chronic renal failure; COPD, chronic obstructive pulmonary disease; LC, liver cirrhosis.
[a] Mann-Whitney U test.
[b] Fisher's exact test.

3.2. The proportion of the patients on enteral nutrition

In our study, all patients were unable to get enteral nutrition on day 1 and 2. On day 3, only 3.2% and 2.1% of the patients in the low-risk and high-risk groups were able to be on enteral nutrition, respectively. On day 7, 58.4% in the low-risk group and 42.7% in the high-risk group were able to get enteral nutrition (Fig. 2).

3.3. Clinical Outcomes and Caloric and Protein Adequacy

There was no significant difference in the daily caloric and protein requirements between the "Early" and the "Usual" groups of patients with high nutritional risk. However, the caloric adequacy of the "Early" group was higher than that of the "Usual" group (0.88 ± 0.34 vs 0.60 ± 0.29; p < 0.001). Moreover, the amount of protein received was higher in the "Early" group than that in the "Usual group" (0.94 ± 0.39 vs 0.47 ± 0.34 g/kg/day; p < 0.001). Graphs presenting daily calorie (via enteral and parenteral routes) and protein administration are provided in a supplementary figure (Supplementary Fig. 1). The "Early" group had lower rates of 30-day mortality (7.6% vs. 26.7%, p = 0.006) and in-hospital mortality (13.6% vs. 28.9%, p = 0.048) than those in the "Usual" group. However, the incidence of infectious complications, including pneumonia, showed no significant difference between the two groups (Table 3).

On the other hand, the patients with low risk of malnutrition had a significant difference in the caloric adequacy (0.72 ± 0.22 vs 0.52 ± 0.22; p < 0.001) and protein supply (0.77 ± 0.43 vs 0.42 ± 0.26 g/kg/day; p < 0.001) between the "Early" and "Usual" groups, yet no significant difference was revealed in terms of length of treatment and mortality. Pneumonia seemed to occur more frequently (21.8% vs. 7.3%; p = 0.004) in the patients who received PN within 48 h in the low nutritional risk group (Supplementary Table 3).

Kaplan–Meier survival curves plotted with the 30-day mortality rates in the high nutritional risk group also showed a statistically significant difference (p = 0.001), while the survival curves of the groups with low nutritional risk did not show a statistically significant difference (p = 0.906) (Fig. 3).

4. Discussion

4.1. Early PN: Perioperative nutritional support in the critically ill surgical patients

Nutritional support is an important strategy for the prevention of malnutrition and has been demonstrated to be beneficial for the survival of critically ill patients [12–14]. Perioperative nutritional support promotes wound healing, lowers the risk of infection, and prevents loss of muscle protein [15–17]. Even in GI surgeries, early initiation of EN has been supported by numerous studies regarding its safety and benefits [18,19]. However, the patients included in the previous studies were relatively healthy participants who underwent elective surgeries. Usually, elective patients do not experience preoperative hypotension, causing possible ischemia-reperfusion injury to the intestine or a cIAI requiring massive irrigation and excessive manipulation of the bowel. In this study, the authors hypothesized that providing adequate calories with PN to critically

Table 2
Initial severity of illness in ED (high-risk group).

	Early (n = 66)	Usual (n = 45)	*p* value
APACHE II, n	15.50 [10.75, 23.00]	17.00 [12.00, 24.00]	0.415[a]
ASA, n (%)			0.709[b]
1	10 (15.2)	8 (17.8)	
2	35 (53.0)	24 (53.3)	
3	21 (31.8)	12 (26.7)	
4	0 (0.0)	1 (2.2)	
qSOFA, n (%)			0.232[b]
0	44 (66.7)	28 (62.2)	
1	16 (24.2)	9 (20.0)	
2	6 (9.1)	5 (11.1)	
3	0 (0.0)	3 (6.7)	
fSOFA, n	4.74 ± 4.22	4.73 ± 3.49	0.990
SIRS, n (%)			0.259[b]
0	6 (9.1)	3 (6.7)	
1	22 (33.3)	8 (17.8)	
2	23 (34.8)	24 (53.3)	
3	14 (21.2)	9 (20.0)	
4	1 (1.5)	1 (2.2)	
SBP, mm/Hg	119.15 ± 26.25	113.87 ± 31.14	0.337
Respiration rate, rpm	18.00 [15.75, 20.00]	16.00 [14.00, 19.50]	0.214[a]
Altered mental status	7 (10.6)	6 (13.3)	0.661
Preoperative hypotension, n (%) mNUTRIC, n	21 (31.8)	20 (44.4)	0.176

ED, emergency department; APACHE II, Acute Physiology and Chronic Health Evaluation II; ASA, American Society of Anesthesiologists; qSOFA, quick sequential organ failure assessment; fSOFA, full sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; SBP, systolic blood pressure; mNUTRIC, modified nutrition risk in critically ill.
[a] Mann-Whitney U test.
[b] Fisher's exact test.

ill surgical patients not eligible for early EN would be associated with lower mortality.

4.2. Early PN administration in patients with high nutritional risk

Since high nutritional risk was reported to be associated with higher mortality in several previous studies [8,20,21], the authors hypothesized that administering PN as early as possible to reduce the chance of malnutrition would be beneficial to increase the survival rates of critically ill patients since most of the enrolled patients were unable to receive early EN. These patients suffered from cIAI, which was followed by GI surgery. Our results showed that the patients who received early PN had more amount of calories and protein administered than those who did not, and had better 30-day and in-hospital survival rates in the high nutritional risk group. However, in the low nutritional risk group, early PN did not affect the clinical outcomes positively. Mortality rates showed no significant difference between the "Early" and "Usual" groups.

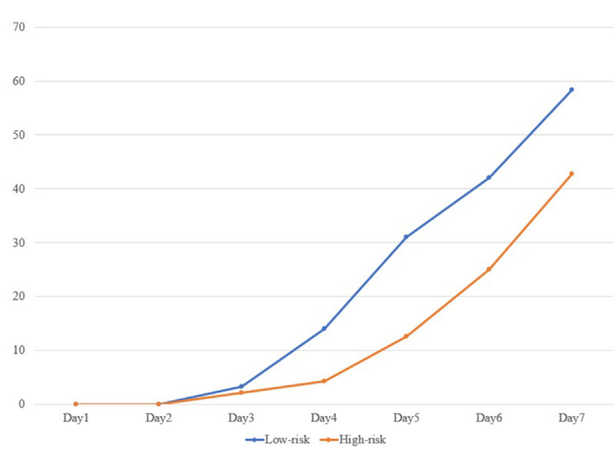

Fig. 2. The proportion of the patient on enteral nutrition each day from day 1 through day 7, presented in percentage.

Table 3
Caloric and protein adequacy and clinical outcomes (high-risk group).

	Early (n = 66)	Usual (n = 45)	*p* value
Caloric requirement, kcal/day	1343.98 ± 277.31	1412.00 ± 314.71	0.232
Protein requirement, g/day	80.64 ± 16.64	84.72 ± 18.88	0.232
Average caloric supply, kcal/day	1125.62 ± 794.99	794.98 ± 302.43	<0.001
Average protein supply, g/day	48.03 ± 15.10	25.62 ± 16.40	<0.001
Caloric adequacy	0.88 ± 0.34	0.60 ± 0.29	<0.001
Protein, g/kg/day	0.94 ± 0.39	0.47 ± 0.34	<0.001
Pneumonia, n (%)	13 (19.7)	11 (24.4)	0.551
Infectious complications, n (%)	36 (54.5)	25 (56.8)	0.814
HLOS, days	20.00 [12.00, 29.00]	13.00 [9.00, 21.00]	0.029[a]
ICU LOS, days	5.00 [1.75, 13.25]	4.00 [2.00, 13.00]	0.894
MV day	1.00 [0.00, 10.00]	3.00 [0.00, 10.00]	0.519
In-hospital mortality, n (%)	9 (13.6)	13 (28.9)	0.048
30-day mortality, n (%)	5 (7.6)	12 (26.7)	0.006

HLOS, hospital length of stay; ICU LOS, intensive care unit length of stay; MV, mechanical ventilation.
[a] Mann-Whitney U test.

4.3. Early PN administration in patients with low nutritional risk

Early PN in patients with low nutritional risk showed a higher rate of newly developed pneumonia in our analysis. It may have resulted from older age and higher CCI score in the group that received early PN. In a previous study, higher infectious complication rates were found in the patient group that received early PN. Furthermore, some studies showed that the patient group with inadequate caloric intake was associated with a higher infectious complication rate. Therefore, both early PN and inadequate caloric intake are likely to result in high infection rates. There is a lack of evidence regarding which postoperative care plan would be ideal for patients not indicated for early EN being at risk for inadequate caloric nourishment and malnutrition. As mentioned above, higher infectious complication rates unrelated to mortality were observed in patients with low nutritional risk in our study. However, in patients with high nutritional risk, early PN was associated with lower infectious complication rates, including pneumonia, though the difference was not statistically significant, and even more, lower mortality rates. According to our result, early supplementary PN can be considered in patients who are critically ill and contraindicated for early EN or those who are unable to reach adequate caloric intake without PN support.

4.4. Tools for nutritional risk stratification

In this study, the mNUTRIC score and BMI were used for risk stratification. Patients who had a high mNUTRIC score or low BMI were considered to have a high risk of malnutrition. Those classified to have a higher nutritional risk consisted of 35.0% of all patients. This percentage was slightly higher but was similar to the previous findings by Braschel et al. [10] and Coltman et al. [22], who reported that 27.7% of their patients were at high nutritional risk. There is no gold standard tool to identify critically ill patients with high nutritional risk. Recently, the NUTRIC and APACHE scores have been reported as good scoring systems that reflect the severity of illness affecting the patients' metabolism, which finally results in malnutrition. Additionally, some studies have shown the association of low BMI with unfavorable outcomes in critically ill patients [23]. In contrast, previous studies presented that the patients with higher BMI showed better outcome in ICU care, which is called

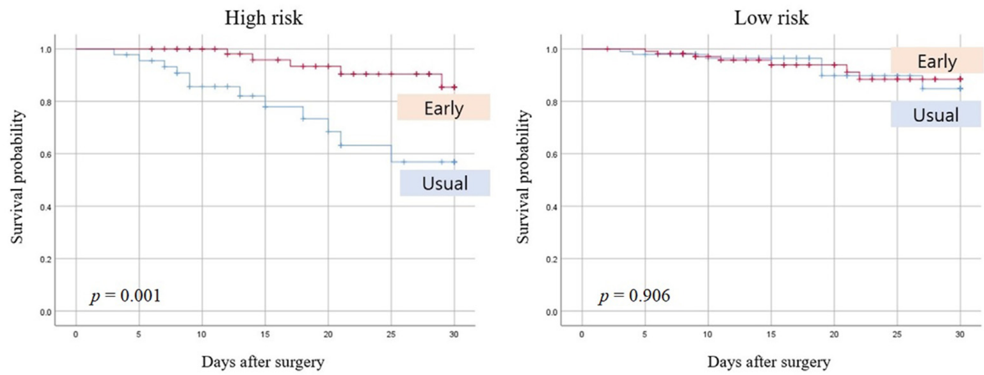

Fig. 3. Kaplan–Meier survival curves for patients with high- and low-nutritional risk.

"Obesity Paradox" [24–27]. In the nutritional aspect, these study results could be due to larger reservoir for overcoming catabolic state and malnutrition in the patients with higher BMI. Thus, for further analysis among the overweight and obese patients, a similar study could be conducted in the North American and European countries to compare the results. The mNUTRIC score and BMI were selected in this study, but more evidence should be accumulated to determine or discover more accurate screening tools to identify critically ill patients at high risk for malnutrition.

4.5. Early PN for adequate caloric support

In a recent study, aggressive nutrition therapy for patients with acute GI injury was beneficial for those with APACHE II scores ≥15 [28]. Similarly, the patients enrolled in this study and assigned to the group with higher nutritional risk had lower mortality rates with early PN administration than those without early PN. European Society for Parenteral and Enteral Nutrition (ESPEN) 2019 guideline also suggests that high-risk patients who are not indicated for early EN should be considered for early supplementary PN for adequate caloric support. This guideline advises a greater use of early supplementary PN than that suggested in the previous guidelines. Patients with high risk of malnutrition, severe illness, or reasons to be administered late EN (high-dose vasopressors, severe bowel edema seen in the operation field, abdominal compartment syndrome, EN intolerance, etc.) should be considered for initiation of early PN. We believe that further studies will support this hypothesis.

4.6. Limitation

The daily requirement of calories was estimated by calculation instead of using an indirect calorimeter. The results would have been more accurate doing so, however, it was practically impossible to use an indirect calorimeter on a daily basis for all patients admitted to our center. Also, this study is based on retrospective analysis of the electronically recorded medical data. Prospective studies or randomized controlled trials should be performed to confirm our study results clearly.

5. Conclusion

Mortality rates in patients at high nutritional risk who received early PN within 48 h after emergency surgery for cIAI was lower than those who did not. Administration of early PN may be necessary for critically ill patients who are unable to achieve their caloric and protein requirements fully with EN alone.

State of authorship

Joohyun Sim and Yun Tae Jung conducted the analysis and produced the first draft of the manuscript. All authors collected the data. Jeong Hong supervised the study. Yun Tae Jung performed the statistical analysis. All authors critically revised the manuscript. This manuscript represents valid work and has not been published elsewhere. All authors have approved the submitted manuscript and account for their contributions.

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Conflict of interest

The authors declare no competing interests.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.10.008.

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