Effect of Early Nutritional Support on Clinical Outcomes of Critically Ill Patients with Sepsis and Septic Shock

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Abstract

Purpose

The initial nutritional delivery policy for patients with sepsis admitted to the intensive care unit (ICU) is not fully elucidated. This study aimed to determine whether initial adequate nutrition supply and route of nutrition delivery during the first week of sepsis onset may improve the clinical outcomes of critically ill septic patients.

Methods

We examined 834 adult patients with sepsis and septic shock in the ICU between November 2013 and May 2017 retrospectively. Poisson log-linear and Cox regressions were performed to assess the relationship between clinical outcomes, sex, modified nutrition risk in the critically ill (mNUTRIC) scores, sequential organ failure assessment and acute physiology and chronic health evaluation scores, route of nutrition delivery, and daily energy and protein delivery during the first week since sepsis onset.

Results

Patients who had higher protein intakes during the first week since sepsis onset had lower in-hospital mortality, while higher energy intakes were associated with lower the 30-day mortality. Route of nutrition delivery was not associated with 1-year mortality in the group with > 70% of the nutritional requirement; however, enteral feeding (EN) with supplemental parenteral nutrition (PN) was superior to only EN or only PN in patients who were underfed.

Conclusion

For patients with sepsis and septic shock, a high daily average protein intake may lower in-hospital mortality and a high energy intake may lower the 30-day mortality, especially for patients with high mNUTRIC scores. For underfed patients, EN with supplemental PN may be better than EN or PN alone.

Introduction

Severe sepsis and septic shock remain frequent syndromes associated with high in-hospital mortality. The mortality rate of patients with severe sepsis and septic shock is 40.4% [1]. Sepsis is a detrimental immune response to an infection that often induces an overwhelming reaction, abolishing the normal reconstitution of immune cell homeostasis [2]. In sepsis, inflammatory mediators serve as potent inducers of catabolism; for example, cytokines play a critical role in breaking down proteins in muscles, promoting bone resorption, and driving lipolysis in adipocytes [3, 4]. Furthermore, inflammation-related endogenous skeletal muscle protein catabolism can quickly progress to severe muscle atrophy, especially early on; it is also associated with immunosuppression, poor wound healing, intensive care unit (ICU)-acquired muscle weakness, and other adverse outcomes [1, 3, 5].

In critically ill patients, the early stages of catabolism might explain why early energy provision up to 70–80% of the measured energy expenditure is apparently associated with improved outcomes [6, 7]. Although the correct amount of protein to be administered to critically ill patients is unknown, doses > 1.2 g/kg are associated with reduced mortality in non-septic non-energy overfed patients in the ICU [6]. Furthermore, a recent large observational study has suggested that achieving ≥ 80% of the prescribed protein intake is associated with decreased mortality in ICU patients [8].

Nutrition therapy for patients with sepsis differs from standard nutritional approaches for critically ill patients. Although the causes for this were not clearly studied, it may be due to infection-caused abnormal host responses that induce progressive physiologic alterations, which consequently limit metabolic capacity by impairing mitochondrial function [9].

Accordingly, the Surviving Sepsis Campaign Guidelines do not recommend the early administration of parenteral nutrition (PN) with or without enteral nutrition (EN) in critically ill patients with sepsis and septic shock who are able to undergo enteral feeding over the first 7 days of sepsis onset [10–12]. However, there is a lack of studies addressing the use of exclusive or supplemental PN early in the acute phase of sepsis [13, 14]. Moreover, Weijs et al. reported that increased protein intakes (1.2 g/kg/d) do not improve outcomes in septic patients compared with non-septic patients [6, 15, 16], although corresponding adverse effects were not found. Furthermore, well-established studies on low energy, low protein nutrition for critically ill septic patients are few.

Moreover, the study included both high-risk patients who needed nutrition and low-risk patients who did not. Therefore, in this study, the Nutrition Risk in Critically Ill (NUTRIC) score was used to quantify the risk of developing worse clinical outcomes that may improve through

intensive and adequate nutritional supports; a high mNUTRIC score indicates better clinical outcomes owing of intensive nutritional support, whereas a low mNUTRIC score indicates minimal benefit from aggressive nutritional support [17].

Therefore, we investigated the effects of nutrition, i.e. energy and protein intake, and route of nutrition delivery during the first 7 days of sepsis onset on clinical prognostic markers such as mortality, ventilator-free days, and ICU and hospital length of stay (LOS). Additionally, the effects of nutritional support on clinical prognosis were examined in the high and low mNUTRIC score groups separately.

Material & Methods

Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of the Seoul National University Bundang Hospital (approval number: B-1907/550-101), which waived the requirement for written informed consent due to the retrospective nature of this study.

Patient population

We included patients aged ≥18 years who had an ICU LOS of over 3 days and experienced sepsis and septic shock in the ICU during 31 November 2013–20 May 2017 at the Seoul National University Bundang Hospital—a tertiary hospital. Patients who died or were discharged from our hospital within 3 days following sepsis onset, pregnant patients, and patients with insufficient medical data to determine whether they had sepsis were excluded. Two intensivists reviewed the electronic medical records (EMR) of 1,382 patients with suspected sepsis and septic shock from the documentation of health care providers or laboratory and physiological data, separately, and excluded 548 patients due to incomplete records or the absence of sepsis and septic shock. A total of 834 patients with sepsis and septic shock were enrolled [18].

Nutritional support

The attending physician of the patients in the ICU determined the amount and type of nutrition to be administered during the daily ICU rounds with the help of a nutrition support team (NST), comprising other intensivists, nurses, a pharmacist and attending ICU pharmacist, and a nutritionist, which provided detailed advice on nutritional support.

Nutrition targets were calculated by NST dietitians, pharmacists, and physicians using the Harrison-Benedict equation, stress factor adjustment, and daily protein requirements based on the American Society for Clinical Nutrition and Metabolism (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines. The condition of each patient, including sedation status, liver and renal function, and malnutrition status, were considered. Daily energy, protein delivery and daily body weight were recorded after ICU admission. The ideal body weight (IBW) was calculated, and if the IBW was lower than the actual body weight (ABW), ABW was used. However, if the opposite was true, we calculated the adjusted body weight.

After achieving hemodynamic stability, EN was preferred over PN. If enteral feeding was not feasible for any reason (such as, gastric residual volume >500 mL, recurrent abdominal discomfort and distension, no bowel sounds, high vasopressor needs, aspiration events, gastrointestinal bleeding, etc.), PN was considered on day 3–5 of fasting or feeding intolerance. PN was reduced or delayed in patients with suspected liver failure, acute kidney injury, or biliary congestion. Protein intakes were to be reduced if blood urea nitrogen levels or creatinine levels without renal replacement therapy increased steeply. Prokinetics was used to promote bowel movement.

Data collection

Data on age, sex, height, weight, body mass index (BMI), daily energy and protein delivery, route of nutrition delivery, comorbidities, microbiological and laboratory results, number of days in which a mechanical ventilator was used, vasopressor use, in-hospital mortality, and ICU LOS and hospital LOS were collected via the EMRs. We calculated 30-day mortality rates following sepsis based on EMR data and the data obtained from the Ministry of the Interior and Safety.

The nutritional data of all patients were collected via EMRs, and the daily amounts of nutrition delivered via parenteral and enteral routes were recorded as daily total energy intake. The protein intake was recorded, and the daily achievement of an energy target (%) and the daily average protein intake was calculated during the first week of sepsis onset. Moreover, the mNUTRIC score, sequential organ failure assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated based on EMR data. The mNUTRIC scores were developed to identify patients in the ICU with a low mortality risk and a small number of days in which a mechanical ventilator was used because of aggressive nutritional therapy. This score included age, BMI, the number of comorbidities, and illness severity (i.e., acute physiology and chronic health evaluation on APACHE II and SOFA scores) upon ICU admission.

Endpoint

The primary endpoint was in-hospital mortality following sepsis onset. Secondary endpoints were 30-day mortality, 1-year mortality, number ventilator-free days within 28 days from sepsis onset, ICU LOS, and hospital LOS following sepsis onset.

Statistical analysis

SPSS version 24 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Categorical variables are expressed as medians (range) and numbers (%) and continuous variables as means (standard deviation). Poisson log-linear regression analysis was used to determine the predictive factors associated with countable clinical outcomes, such as the number of ventilator-free days within 28 days of sepsis onset and ICU LOS and hospital LOS. Independent variables included sex, mNUTRIC, SOFA and APACHE II scores, daily average achievement of an energy target (%), and average protein intake during the first week of sepsis onset. Patients who died before ventilator cessation or were discharged from the ICU or hospital were not included in this analysis to eliminate bias.

A Cox regression analysis was used to determine whether mortality was associated with sex, mNUTRIC, SOFA, and APACHE II scores, route of nutrition delivery, daily average achievement of an energy target, and average protein intake during the first week of sepsis onset. Univariable analyses were performed first, and factors with P <0.05 were selected for multivariable analyses. In each multivariable analysis, we used a backwards stepwise regression approach to eliminate the predictors that did not independently contribute to 30-day and in-hospital mortalities. Odds ratios and hazards ratios (HRs) with their 95% confidence intervals (CIs) were calculated. A P-value < 0.05 was considered significant.

Results

A total of 834 patients in the ICU with sepsis and septic shock were included. The demographic, physiologic, and nutritional data and clinical outcomes of all patients are displayed in Table 1. The mean age was 68.9 years, and 65.5% of patients were male. The mean SOFA and APACHE II scores were 10.8 ± 3.7 and 32.0 ± 8.4, respectively. The mean number of days in which a mechanical ventilator was used was 8.4 ± 23.3 days, and the mean ICU LOS and hospital LOS were 13.2 ± 13.7 and 35.6 ± 42.3 days, respectively.

The most common source of infection was respiratory (57.6%), followed by the gastrointestinal entrance (15.1%). Furthermore, gram-negative pathogens were the most common (32.3%). The in-hospital and 30-day mortality rates were 33.7% (n=281) and 28.8% (n=240), respectively. The mean mNUTRIC score was 6.7±1.7, and 89.9% of patients were in the high-score group (5–9 points). The mean number of days on vasopressors, such as norepinephrine, was 7.1± 9.3 days.

As for the nutrition delivered during first week of sepsis, average daily energy achievements of target energy were 80.0±33.7%, and the average daily protein intake during the first week of sepsis onset was 0.64 ± 0.43 g/kg/day. Figure 1 shows the pattern of daily energy delivery (kcal) via enteral and parenteral feeding, and daily protein intake (g/kg) during the first week of sepsis onset.

Clinical outcomes

In-hospital mortality and nutrition supply

The association of in-hospital mortality and nutrition supply are outlined in Table 2. When analysed using the univariable Cox regression analysis, the average daily protein intake and average energy intake were significantly associated with reduced in-hospital mortality (HR, 0.43; 95% CI, 0.30–0.60; and P <0.001; and HR, 0.93; 95% CI, 0.90–0.96; and P <0.001), respectively. Increases in mNUTRIC (HR, 1.25; 95% CI, 1.16–1.36; and P<0.001), SOFA (HR, 1.14; 95% CI, 1.10–1.18; and P <0.001), and APACHE II scores (HR, 1.05; 95% CI, 1.04–1.07; and P <0.001) were associated with increases in in-hospital mortality. Sex and number of co-morbidities were not significantly associated with in-hospital mortality.

A multivariable Cox regression analysis was performed using the average daily protein intake, average energy intake, and mNUTRIC, SOFA, and APACHE II scores. The increased average daily protein intake during the first week of sepsis onset, mNUTRIC and SOFA scores were associated with reduced in-hospital mortality (HR, 0.55; 95% CI, 0.39–0.78; and P=0.001; HR, 1.11; 95% CI, 1.01–1.23; P=0.039; and HR, 1.07; 95% CI, 1.02–1.12; and p=0.006), respectively.

Comparison of in-hospital mortality between the low and high mNUTRIC score groups

When analysed using the univariable Cox regression analysis, no factor was associated with in-hospital mortality in the low mNUTRIC score group. In contrast, the average daily protein intake and average energy intake were significantly associated with reduced in-hospital mortality in the high mNUTRIC score group, (HR, 0.46; 95% CI, 0.32–0.65; P <0.001; and HR, 0.93; 95% CI, 0.89–0.96; and P<0.001), respectively. Additionally, increases in the SOFA and APACHE II scores were associated with increases in in-hospital mortality (HR, 1.12; 95% CI, 1.08–1.16; and P <0.001; and HR, 1.05; 95% CI, 1.03–1.16; and P<0.001), respectively.

A multivariable Cox regression analysis was performed using the average daily protein intake, average energy intake, and SOFA and APACHE II scores. Increases in daily protein intake during the first week of sepsis onset, and increases in the SOFA, and APACHE II scores were associated with reduced in-hospital mortality in the high mNUTRIC score group, (HR, 0.59; 95% CI, 0.42–0.84; P=0.004; HR, 1.07; 95% CI, 1.02–1.12; and P=0.009; and HR, 1.03; 95% CI, 1.01–1.05; and P=0.015), respectively.

30-day mortality and nutrition supply

The association between 30-day mortality and nutrition supply are outlined in Table 3. A univariate Cox regression analysis has shown that the average daily protein intake, daily energy intake, mNUTRIC, SOFA, and APACHE II scores, and the number of co-morbidities were significantly associated with lower 30-day mortality. Furthermore, increases in daily energy intake was associated with lower 30-day mortality in the multivariable regression analysis after adjusting for mNUTRIC, SOFA, and APACHE II scores, and the number of co-morbidities.

Comparison of 30-day mortality between the low and high mNUTRIC score groups

In the low mNUTRIC score group, there were no associations between protein or energy intake with 30-day mortality. However, in the high mNUTRIC score group, a univariate regression analysis has shown that both daily energy and protein intakes were associated with lower 30-day mortality. Moreover, increased average daily energy intakes were associated with reduced 30-day mortality in the high mNUTRIC score group as a result of a multivariate regression analysis (HR, 0.96; 95% CI, 0.92–1.00; and P=0.026).

Ventilator-free days within 28 days of sepsis onset and nutritional support

A univariate Poisson log linear regression analysis has shown that the average daily protein and energy intakes were not significantly related to the number of ventilator-free days within 28 days of sepsis onset.
Comparison of number of ventilator-free days within 28 days of sepsis onset between the high and low mNUTRIC score group

In the low mNUTRIC score group, the average daily protein and energy intakes were not significantly associated with the number of ventilator-free days within 28 days of sepsis onset on a univariate Poisson log linear analysis. In contrast, patients in the high NUTRIC score group had a significantly longer ventilator-free days within 28 days of sepsis onset when higher daily average energy intakes were administered, as assessed using a Poisson log linear regression analysis. However, a multivariable Poisson log linear regression analysis using the APACHE II and SOFA scores did not demonstrate the aforementioned association.

Length of stay in the ICU and hospital and nutritional support

When analysed using the univariate Poisson log linear regression analysis, the average daily protein intake and energy intake were significantly associated with reduced LOS in the ICU, and in the hospital, (HR, 0.35; 95% CI, 0.22-0.54; and P <0.001; HR, 0.90; 95% CI, 0.90-0.94; and P<0.001), and (HR, 0.48; 95% CI, 0.34-0.67; and P <0.001; HR, 0.93; 95% CI, 0.90-0.97; and P<0.001), respectively. However, a multivariate Poisson log linear regression analysis showed that the amount of energy intake and protein intake were associated with a relatively low ICU LOS.

1-year mortality and route of nutrition delivery

A Kaplan–Meier estimate analysis showed that route of nutrition delivery during the first week of sepsis onset was not associated with 1-year mortality in the group met >70% of their daily energy intake requirement. However, EN with supplemental PN was superior to only EN (P=0.016) or only PN (P=0.042) in the patients who had been underfed (≤70% of energy target) (Figure 2). Cox-regression analysis adjusted with APACHE II score, mNUTRIC score, SOFA score, the number of co-morbidities, and amount of daily energy intake, revealed that during first week of sepsis (P=0.026), EN with supplemental PN was superior to EN in improving 1-year mortality (Table 4).

Discussion

Although the crucial implications of nutritional supply in patients have been reported in many studies, the relationship of nutritional supply and route with prognosis in critically ill patients with sepsis and septic shock remain insufficient. The significance of this study is that it comprises 834 critically ill patients with sepsis and septic shock. In this study, protein intake increments of 0.1 g/kg/day during the first week of sepsis onset were associated with a 6% reduction in in-hospital mortality, especially in the high mNUTRIC group. Increases in daily energy intake were associated with lower 30-day mortality, especially in the high mNUTRIC score group. Furthermore, EN with supplemental PN was superior to EN to improve 1-year mortality during first week of sepsis onset.

These findings might be new or different from previous studies [16, 19]. The main reason could be a difference in characteristics of patients enrolled in the studies. For instance, the patients in this study all had sepsis or septic shock, were old-aged (median value: 72 years), had high

APACHE II, SOFA, and mNUTRIC scores (median values: 32, 11, and 7, respectively), and high in-hospital mortality (33.7%) and 30-day mortality (28.8%). In contrast, other studies about nutrition and critically ill patients included fewer patients who had sepsis (7–22%), were younger than 70 years, had lower APACHE II, SOFA, and mNUTRIC scores (21–26, 8–9, and 4–5, respectively), and had 13–48% of in-hospital mortality [19-21].

While experts have agreed that the route of nutrition delivery matters, there is no consensus on which route is better for septic patients in the ICU. Although the ASPEN guidelines suggest that critically ill patients receive EN therapy within 24–48 hours of making the diagnosis of severe sepsis or septic shock, and avoid the usage of exclusive PN or supplemental PN in conjunction with EN early in the acute phase of severe sepsis or septic shock, there was no definite evidence to support the benefit of EN over PN according to mortality [22]. In this study, we divided the patients into three groups: 1) EN group, 2) PN group, and 3) EN with supplemental PN; because the PN group has high possibility of contraindication with EN. We compared these three groups according to 1-year mortality, and the Cox-regression analysis revealed that EN with supplemental PN was superior to EN in improving 1-year mortality during the first week of sepsis, even after adjusting the energy intake amount and patient severity scores. Furthermore, Kaplan–Meier curves for 1-year mortality according to route of nutrition delivery in the low and high energy intake groups showed that EN with supplemental PN was superior to only EN or only PN in critically ill septic patients who fed with under 70% of the nutrition requirement (Figure 2). In contrast, route of nutrition supply was not associated with 1-year mortality in the group who had energy over 70% of the nutrition requirement. These results suggest that adequate energy intake might be more important than route of nutrition delivery, however, patients who receive inadequate energy may benefit from EN with supplemental PN, rather EN or PN alone. In the NUTRIREA-2 study, enrolled shock patients with a high SOFA score (11) and in-hospital mortality (36%), which were similar to this study, revealed that early EN did not result in reduced mortality or secondary infection when compared with PN. However, this result cannot be directly applied to septic patients exclusively, because although the patients included in this study had similar patient severity with our study, only 61–64% of their patients had septic shock [22]. Moreover, because of a multicentre RCT including 33 English ICUs, Harvey et al. found no significant difference in 30-day mortality associated with the route of delivery of early nutritional support in adult patients whose mean APACHE II score was 19, SOFA score 9.5, and hospital mortality at around 36-38%. However, this study did not include the proportion of patients with sepsis [14].

Increases in daily energy intake was associated with lower 30-day mortality and in-hospital mortality before and after adjustment with patient severity scores and amount of daily protein intake. In the prospective study of Hung et al. on 151 septic patients, they found that the septic patients with insufficient nutrition had poor prognosis despite being immunocompetent. [23]. However, the number of patients involved was small (low energy group [n=16] vs. high energy group [n=69]). Additionally, the SOFA score of the low energy group was higher than the high energy group, and the study did not adjust the SOFA score.

Increases in daily protein intake was also associated with reduced 30-day mortality and in-hospital mortality before adjustment with patient severity scores and amount of energy received per day. Higher daily protein intake seemed to have a relation with improved outcomes upon discharge from the hospital, after adjustment. For instance, a retrospective cohort study by Bendavid, et al. has revealed that early protein provision in critically ill patients might be associated with improved survival, even after adjusting for confounders. Furthermore, a single centre cohort study by Weijs, et al. also showed that medical ICU patients with improvements in daily protein intake during hospitalisation have decreased odds of mortality in the 3 months following hospital discharge. However, in both studies, patients with sepsis only comprised 17% and 21% of the study population, respectively [3, 20].

An important characteristic of patients in this study was that they were not over-fed: the average amount of energy delivered during the first week of sepsis was, in median values, 923.6 (663.7–1165.1) kcal and 80.0% of basal energy expenditure in this study. Additionally, the average protein supply during the first week following sepsis diagnosis was 0.62 g/kg/day, which is lower than the protein limit of 0.8 g/kg/day recommended by the ASPEN guidelines [13, 20]. For that reason, in critically ill patients with sepsis, EN is generally limited due to excessive vasopressor use [21], as ischaemia of bowels can occur due to shock state. Second, supplemental PN is often not recommended or allowed in cases of multi-organ failure including haptic or renal injury. Finally, we also determined amount of energy with reference to the ASPEN/SCCM or ESPEN guidelines. The ASPEN/SCCM guidelines recommend increasing the amount of energy during the first week after initially trying trophic feeding for critically ill patients with sepsis [20]. While the ESPEN guidelines recommend low-calorie nutrition at a level of 70% of 25–30 kcal/body weight per day to critically ill patients with sepsis [12]. This should be overcome in future studies through RCT.

Our study presents several limitations. First, this was a relatively small single-centre study. However, we achieved statistical significance and used strict selection criteria. Second, as data on patients were obtained for over 3 years, which is a relatively long period, management and faculty may have changed, and this is significant because nutritional support aggressiveness depends on the attending physician’s decision and discretion. NST also conducts regular ICU rounds and provides continuous guidance on the nutrition plan. Therefore, the nutritional support provided in the ICU may have remained relatively consistent. The third limitation is the presence of unavoidable bias due to the retrospective nature of the study.

Conclusions

In critically ill septic patients, the mortality decreased as the amount of protein or caloric supply increased during the initial first week of sepsis onset. Additionally, EN with supplemental PN might be a better route of nutrition delivery than EN or PN alone for septic patients in the ICU.

Declarations

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Conflicts of Interest. Competing interests: All authors declare that they have no conflicts of interest.

Availability of data and material (data transparency)

Code availability (software application or custom code)

Author contributions:

Designed the study and drafted the manuscript: JKC, HSK, and IAS
Data acquisition: JKC, IAS, EL, and EJK
Data analysis: IAS, EJK, and JKC
Data interpretation and critical revisions of the paper: JKC, HSK, IAS, EL, and JHL
All authors approved the final version of the manuscript.

Ethics approval: This study was approved by the institutional review board of the Seoul National University Bundang Hospital (approval number: B-1907/550-101).

Consent to participate: The requirement for written informed consent was waived due to the retrospective nature of the study.

Consent for publication (include appropriate statements)

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Tables

Table 1
Baseline characteristics and clinical outcomes of patients

Characteristic	Total (N = 834)
Sex, male	546 (65.5%)
Age (years)	72 (62.0–78.3)
BMI (kg/m^2)	21.3 (18.5–24.1)
SOFA score	11.0 (8.8–13.0)
APACHE II score	32.0 (26.0–38.0)
Days from hospital to ICU admission ≥ 1 day	445 (53.4%)
mNUTRIC scores	7 (6–8)
Low score (0–4 points)	84 (10.1%)
High score (5–9 points)	750 (89.9%)
Comorbidities	2 (1–4)
Myocardial disease	216 (25.9)
Peripheral vascular disease	438 (52.5%)
Pulmonary disease	139 (16.7%)
Neurologic disease	161 (19.3%)
Endocrinal disease	233 (27.9%)
Chronic renal disease	108 (12.9%)
Previous HD	41 (4.9%)
Gastrointestinal disease	82 (9.8%)
Cancer/immunocompromised state	267 (32.0%)
Psychological disease	24 (2.9%)
Musculoskeletal disease	86 (10.3%)
Substance use disorder	27 (3.2%)
Miscellaneous	26 (3.1%)
Types of intensive care units (ICUs)	
Medical ICU	578 (69.3%)
Surgical ICU	103 (12.4%)
Emergency ICU	93 (11.2%)
Neuro/neurosurgical ICU	60 (7.2%)
Source of infection	
Respiratory infection	480 (57.6%)
Genitourinary infection	41 (4.9%)
Gastrointestinal infection	126 (15.1%)
Other infections	115 (13.8%)
Multiple infection	53 (6.4%)
Unknown source of infection	19 (2.3%)

Numbers are presented as median (interquartile range) or number (percentage). BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; BMI, body mass index; and mNUTRIC, modified Nutrition Risk in the Critically Ill

Characteristic	Total (N = 834)
Pathogen type	
Gram-positive pathogens	176 (21.1%)
Gram-negative pathogens	269 (32.3%)
Other	12 (1.4%)
Multi-microbial infections	125 (15.0%)
Fungi	30 (3.6%)
Viruses	27 (3.2%)
Unidentified pathogens	195 (23.4%)
Nutrition	
Number of days in which the energy target of 70% was achieved	2 (2–4)
Average daily protein intake per body weight during the first week of sepsis onset (g/kg/day)	0.62 (0.37–0.87)
Average daily protein intake during the first week of sepsis onset (g/day).	35.0 (21.3–47.4)
Average daily energy intake during the first week of sepsis onset (Kcal/day).	923.6 (663.7–1165.1)
Average target energy achievement during the first week of sepsis onset (%).	80.3 (56.1–99.8)
Treatment in ICU	
The mean number of ICU days on any vasopressor following sepsis onset	5 (2–8)
The mean number of mechanical ventilator (days) following sepsis onset	3 (0–9)
Vasopressor free days during 28 days following sepsis onset	23 (14–26)
Clinical outcomes	
Length of ICU stay (days) following sepsis onset	9 (6–15)
Length of hospital stay (days) following sepsis onset	25 (14–43)
In-ICU mortality	175 (21.0%)
In-hospital mortality	281 (33.7%)
30-day mortality	240 (28.8%)
1-year mortality	488 (58.5%)
Discharge course	
Other hospital	211 (25.3%)
Healthcare centre	58 (7.0%)
Home	276 (33.1%)
Death	280 (33.6%)
Other courses	9 (1.1%)

Numbers are presented as median (interquartile range) or number (percentage). BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; BMI, body mass index; and mNUTRIC, modified Nutrition Risk in the Critically Ill

Table 2
Association between in-hospital mortality and nutrition delivered to septic patients for the first week after the onset of sepsis in intensive care units

	Total (N = 834)				mNUTRIC scores							
					Low (N = 84)				High (N = 750)			
	Unadjusted		Adjusted†		Unadjusted		Adjusted†		Unadjusted		Adjusted†	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Sex, male	1.11 (0.86–1.43)	0.412			0.77 (0.18–3.28)	0.727			1.11 (0.86–1.44)	0.413		
SOFA score	1.14 (1.10–1.18)	< 0.001*	1.07 (1.02–1.12)	0.006*	1.15 (1.00–1.34)	0.065			1.12 (1.08–1.16)	< 0.001*	1.07 (1.02–1.12)	0.009*
APACHE II score	1.05 (1.04–1.07)	< 0.001*	1.02 (1.00–1.04)	0.083	1.00 (0.89–1.12)	0.971			1.05 (1.03–1.06)	< 0.001*	1.03 (1.01–1.05)	0.015 *
Comorbidities	1.06 (1.00–1.13)	0.070			1.01 (0.61–1.68)	0.975			1.03 (0.96–1.10)	0.457		
Average daily protein intake per body weight (g/kg/day)	0.43 (0.30–0.60)	< 0.001*	0.55 (0.39–0.78)	0.001*	0.22 (0.03–1.50)	0.121			0.46 (0.32–0.65)	< 0.001*	0.59 (0.42–0.84)	0.004*
Average daily energy intake, target 10% days 1–7	0.93 (0.90–0.96)	< 0.001*			0.88 (0.71–1.09)	0.250			0.93 (0.89–0.96)	< 0.001*		
mNUTRIC score	1.25 (1.16–1.36)	< 0.001*	1.11 (1.01–1.23)	0.039*								

CI, Confidence Interval; mNUTRIC, modified Nutrition Risk in the Critically Ill; SOFA, Sequential Organ Failure Assessment score; and APACHE II, Acute Physiology and Chronic Health Evaluation II

* $p < 0.05$ was considered significant statistically.

† A multivariable Cox regression analysis was performed using risk factors ($p < 0.05$) obtained from the univariable Cox regression analysis.

Table 3
Association between 30-day mortality and nutrition delivered for the first week following sepsis or septic shock onset in intensive care units

	Total (N = 834)				mNUTRIC score							
					Low (N = 84)				High (N = 750)			
	Unadjusted		Adjusted†		Unadjusted		Adjusted†		Unadjusted		Adjusted†	
	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value
Sex, male	1.17 [0.89–1.54]	0.249			1.30 [1.10–1.53]	0.002*	1.28 [1.08–1.53]	0.006*	1.13 [1.09–1.18]	< 0.001*	1.07 [1.02–1.13]	0.010*
SOFA score	1.06 [1.05–1.08]	< 0.001*	1.07 [1.02–1.13]	0.009*	1.06 [0.92–1.21]	0.390			1.05 [1.04–1.07]	< 0.001*	1.03 [1.01–1.06]	0.003*
APACHE II score	1.36 [1.24–1.50]	< 0.001*	1.02 [1.00–1.05]	0.049*	0.89 [0.43–1.83]	0.749			1.05 [0.98–1.13]	0.184		
Comorbidities	1.09 [1.02–1.17]	0.016*			0.10 [0.01–2.03]	0.132			0.51 [0.35–0.73]	< 0.001*		
Average daily protein intake per body weight (g/kg/day)	0.47 [0.32–0.68]	< 0.001*			0.70 [0.49–0.99]	0.043*	0.71 [0.48–1.05]	0.084	0.93 [0.89–0.97]	< 0.001*	0.96 [0.92–1.00]	0.026*
Average daily energy intake, target 10% days 1–7	0.92 [0.89–0.96]	< 0.001*	0.94 [0.90–0.98]	0.003*	0.98 [0.18–5.36]	0.983			1.19 [0.90–1.57]	0.220		
mNUTRIC score	1.16 [1.12–1.20]	< 0.001*	1.21 [1.08–1.36]	0.001*								

CI, Confidence Interval; mNUTRIC, modified Nutrition Risk in the Critically Ill; SOFA, Sequential Organ Failure Assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II

* $p < 0.05$ was considered significant statistically

† A multivariable Cox regression analysis was performed using risk factors ($p < 0.05$) obtained from the univariable Cox regression analysis.

Table 4
Association of delivery route of nutrition with 1-year mortality in patients with sepsis or septic shock in intensive care units

	Total (N = 827)			
	Unadjusted		Adjusted†	
	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value
Sex, male	1.29 [1.07–1.57]	0.009*	0.75 [0.62–0.92]	0.004*
SOFA score	1.10 [1.08–1.13]	< 0.001*		
APACHE II score	1.05 [1.04–1.06]	< 0.001*	1.03 [1.02–1.05]	< 0.001*
Comorbidities	1.12 [10.7–1.18]	< 0.001*	1.06 [1.01–1.13]	0.034*
mNUTRIC score	1.25 [1.18–1.33]	< 0.001*	1.11 [1.03–1.21]	0.008*
Average daily energy intake, target 10% days 1–7	0.97 [0.94–0.99]	0.013*	0.97 [0.94–1.00]	0.032*
Route of nutrition delivery		0.005*		0.067
EN	1.46 [1.16–1.84]	< 0.001**	1.31 [1.03–1.65]	0.026**
PN	1.19 [0.97–1.47]	0.093	1.16 [0.94–1.42]	0.171
EN with supplemental PN	1		1	
CI, confidence interval; mNUTRIC, modified nutrition risk in the critically ill; SOFA, Sequential Organ Failure Assessment score; APACHE II, Acute Physiology and Chronic Health Evaluation II, EN, enteral feeding; PN, parenteral feeding				
* p < 0.05 was considered significant statistically				
**P < 0.05 compared with EN with supplemental PN				
† A multivariable Cox regression analysis was performed using risk factors (p < 0.05) obtained from the univariable Cox regression analysis				

Figures

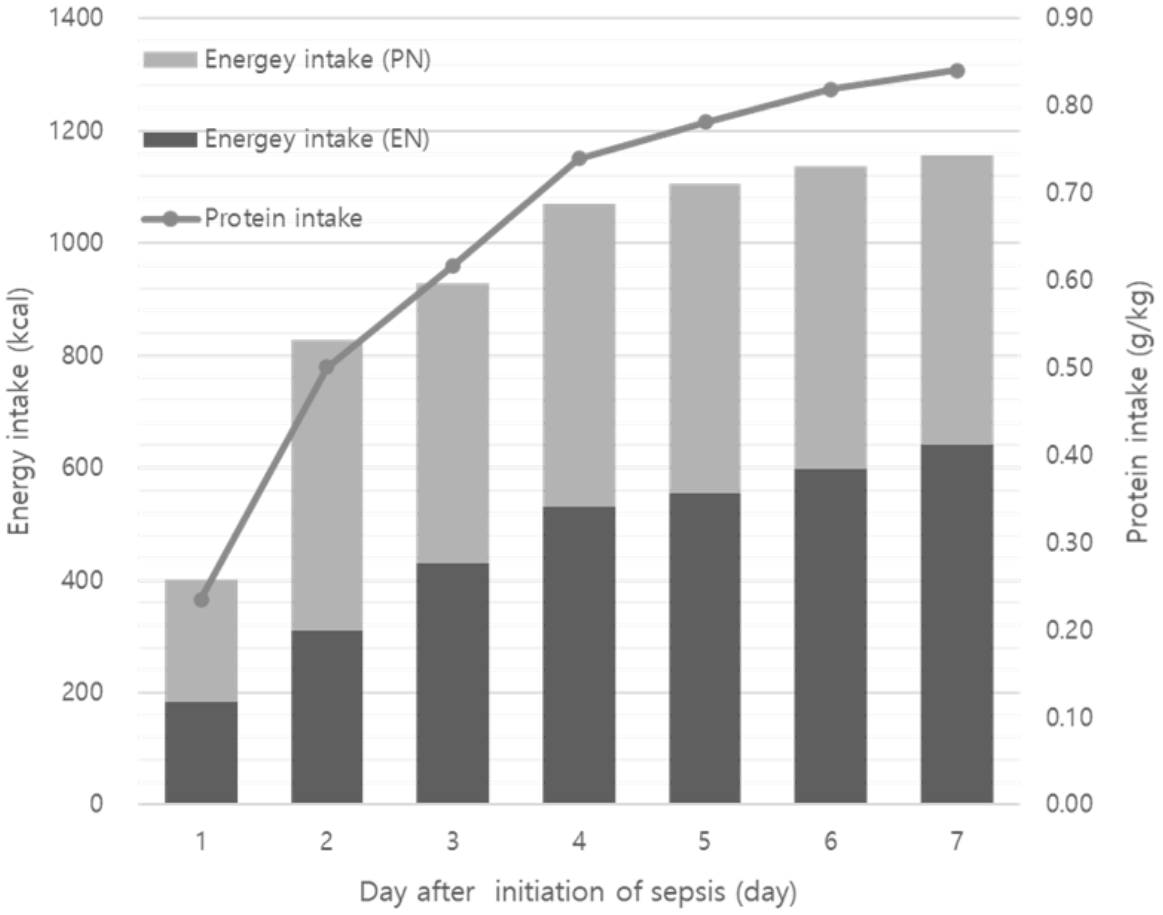

Figure 1

Daily energy (kcal) and protein (g/kg) supplied to patients following sepsis and septic shock onset Column height represents the mean daily energy received (kcal). PN is indicated in light grey and EN in dark grey. Grey dots and lines represent protein intake (g/kg). EN, enteral nutrition; and PN, parenteral nutrition

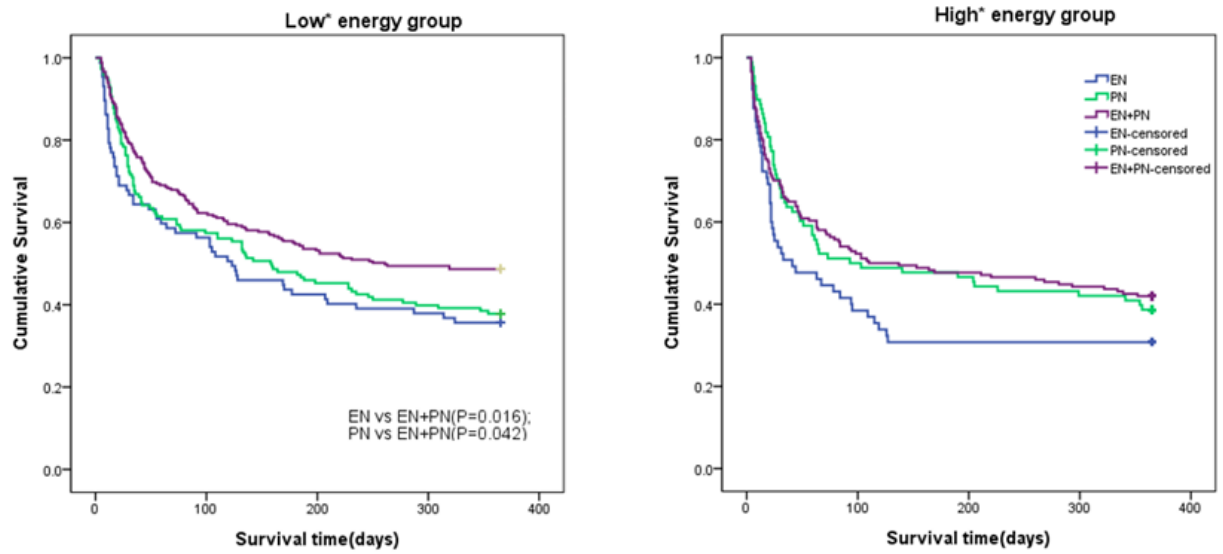

Figure 2

Kaplan–Meier curves for 1-year mortality according to route of nutrition delivery in the groups of low and high energy intake comprising the critically ill septic patients. *Low energy group: EN with supplemental PN was superior to only EN (P=0.016) or only PN (P=0.042) in the patients fed with < 70% of the nutrition requirement; high energy group: route of nutrition supply was not associated with 1-year mortality in the group with energy > 70% of the nutrition requirement. EN is indicated by the blue line, PN by the green line, and EN with supplemental PN by the purple line EN, enteral nutrition; and PN, parenteral nutrition