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Optimizing nitrogen balance is associated with better outcomes in neurocritically ill patients

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Abstract

Background Marked protein catabolism is common in patients with critical illness. We hypothesized that optimal protein supplementation using nitrogen balance might be associated with better clinical outcomes in patients in the neurointensive care unit (NICU).

Methods A retrospective observational analysis was performed among patients admitted to the NICU between July 2017 and December 2018. Nitrogen balance was measured within 72 hours after NICU admission and measurements were repeated after 10 days in those who stayed in the NICU for more than 7 days. Nitrogen balance was calculated using a standard formula: total protein intake (grams)/6.25 – (urine urea nitrogen + 4 grams). Included patients were categorized into two groups (positive or negative) based on the initial nitrogen balance results. The rate of neurological worsening, defined by a worsening of ≥2 in the Glasgow Coma Scale (GCS) score, and in-hospital mortality were compared between patients who achieved the improvement of nitrogen balance on a follow-up measurement and those who failed to.

Results A total of 175 patients were included, and 140 (80.0%) had a negative nitrogen balance on the initial assessment. The negative nitrogen balance group had a lower GCS, longer NICU stay, more events of neurological worsening, and higher in-hospital mortality. Among the 77 patients (44.0%) who underwent a follow-up measurement of nitrogen balance (on a median day of 10), 39 (50.6%) showed an improvement in nitrogen balance and thus received a higher amount of protein (1.94 g/kg/day) than those who did not show this improvement (1.28 g/kg/day) ($P < 0.001$). The improvement group had fewer events of neurological worsening (15.4% vs. 36.8%, $P = 0.032$) and lower in-hospital mortality (12.8% vs. 31.6%, $P = 0.047$). However, there were no significant differences in baseline nitrogen balance, GCS, and the development of acute kidney injury between the two groups.

Conclusions This study demonstrated that a significant proportion of patients in NICU were under protein hypercatabolism. An adequate provision of protein was associated with improved outcomes, suggesting the importance of protein supplementation in neurocritically ill patients.

Background

Systemic inflammatory responses (SIR), elicited by acute brain injury, may lead to an alteration in metabolic homeostasis [1]. Insufficient caloric intake has been linked to an increase in morbidity and mortality in patients with severe brain damage [2–6]. Moreover, recent studies suggest that protein balance is more important than the total amount of caloric intake in patients in critical conditions [5, 7–11]. Protein catabolism, triggered by SIR, may result in the depletion of amino acids essential for cellular or tissue repair and therefore may result in long-term metabolic dysfunction [4, 12–14]. Despite this evidence, proteins have not been sufficiently supplemented in critically ill patients who require treatment in the neurointensive care unit (NICU) [4, 15].

Nutritional protein balance can be simply assessed using nitrogen balance, calculated from protein intake and urinary nitrogen output [16, 17]. Although the optimal amount of protein intake in the NICU has not

been determined, an individualized nutritional approach to minimize negative protein balance might be beneficial for such patients. Therefore, we aimed to investigate the association between nitrogen balance and clinical outcomes in patients in the NICU.

Methods

Study population

We retrospectively identified a consecutive series of patients admitted to the NICU at our institution between July 2017 and December 2018. Inclusion criteria were 1) age older than 18 years, 2) NICU admission with an expected stay of more than 72 hours, and 3) available data on urine urea nitrogen (UUN) measured within 72 hours after NICU admission using a 24-hour urine collection. Among the patients who stayed in the NICU for more than 7 days, a follow-up UUN measurement was performed. This study was approved by the Institutional Review Board (IRB NO H-1908-072-1054).

Baseline characteristics and clinical information

Baseline characteristics including age, sex, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and atrial fibrillation; and a history of stroke/transient ischemic attack were evaluated. In addition, we obtained information regarding malignancy and gastrointestinal diseases related to the nutritional status. Laboratory evaluations were performed for blood urea nitrogen (BUN) and creatinine (Cr). We also assessed the primary diagnosis at NICU admission and the treatment process which might affect energy metabolism (i.e,, barbiturate coma therapy, sedation, targeted temperature management [TTM], craniectomy/craniotomy, and use of anticonvulsant therapy in status epilepticus). Severity of the patient's condition at admission was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE)-II score, and neurological assessments were performed using the Glasgow Coma Scale (GCS) during NICU hospitalization.

Nutrition support with monitoring

Protein intake (g/kg/day) and caloric intake (kcal/kg/day) were assessed daily during NICU hospitalization based on the amount of enteral nutrition (EN) or parenteral nutrition (PN), and types of fluid. The methods of nutrition delivery (EN, PN, a combination of EN and PN, and nil per os [NPO]) was also assessed. Moreover, we calculated nitrogen balance using the protein intake and 24-hour UUN data (grams of nitrogen excreted in urine over a 24-hour period). The following standard formula was used: total protein intake (g)/6.25 – (UUN + 4 g) [16, 17]. Patients were divided into two groups based on the initial nitrogen balance results (positive protein anabolism or negative protein catabolism). A follow-up nitrogen balance measurement was performed among patients who stayed in the NICU for more 7 days. Those patients were categorized into two groups based on the results of the follow-up nitrogen balance examination (improvement group; zero or positive nitrogen balance vs. failure to improve group; persistent negative nitrogen balance). Cumulative fluid balance was also assessed using input (I) and output (O) during the same period. Body weight, height, body mass index (BMI), and the percentage of

ideal body weight were assessed on admission. Body weight change was also monitored during the protein monitoring period, and weight loss was defined as a decrease in body weight of more than 3 kg or 5% as compared to baseline [18, 19].

Outcome assessments

The primary outcome was neurological worsening during NICU hospitalization, defined as an aggravation of ≥ 2 points compared to the baseline in the GCS score [20]. Secondary outcomes were in-hospital mortality, ICU or hospital length of stay, and development of acute kidney injury (AKI), which was determined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [21].

Statistical analysis

Baseline characteristics are presented as frequency (%) and continuous variables with normal distributions are presented as mean ± standard deviation (SD), while variables that were not normally distributed are presented as median (interquartile range, IQR). Continuous variables were compared using the Student's t-tests or the Mann–Whitney U-test, and the proportions of categorical variables were compared using the Pearson's χ^2 tests or the Fisher's exact test, as appropriate, to evaluate the relationship between protein balance and outcomes. Moreover, the Kaplan-Meier method was used to compare outcomes and timings between the patients with and without improvement of protein balance. For all analyses, a 2-tailed P value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS program (Version 25.0, IBM Statistics), and GraphPad Prism (Version 8, GraphPad Software, San Diego, CA, USA).

Results

Among a total of 175 patients (male, 50.3%; mean age, 59.5 years), 140 patients (80.0%) had a negative nitrogen balance on initial assessment (Table 1). The negative nitrogen balance group was more likely to have lower initial GCS and undergo additional treatments including propofol or barbiturate coma therapy, TTM, and decompressive surgery. Regarding nutritional variables, higher protein and calories were supplemented in patients with positive nitrogen balance than in those with negative nitrogen balance (protein: 1.58 ± 0.40 vs. 0.58 ± 0.48 g/kg/day, P < 0.001; calories: 25.6 ± 7.3 vs. 11.7 ± 9.5 kcal/kg/day, P < 0.001). In addition, EN was a dominant form of nutritional support in the positive balance group, while NPO was more frequent in the negative balance group (P = 0.002, Table 1). The time of the first UUN measurement after NICU admission was not different between the two groups (median, 3 [2.0–4.0] days vs. 4, [2.0-6.75] days, P = 0.065). The percentage of patients with neurological worsening (5.7% vs. 23.4%, P = 0.015) and in-hospital mortality (5.7% vs. 20.0%, P = 0.045) was significantly higher in the group with negative nitrogen balance. Moreover, patients with negative nitrogen balance had longer NICU length of stay (13, IQR [7–22] vs. 4, IQR [3–11], P < 0.001) and hospital length of stay (28, IQR [18.25–49.5] vs. 19, IQR [12–29] P = 0.002) than those with positive nitrogen balance.

Table 1

Clinical characteristics according to initial nitrogen balance

	Positive nitrogen balance (n = 35, 20.0%)	Negative nitrogen balance (n = 140, 80.0%)	P-value
Age, mean (SD), year	56.4 ± 15.7	60.3 ± 18.1	0.246
Male, n (%)	13 (37.1)	75 (53.6)	0.082
BMI, mean (SD), kg/m2	22.5 ± 3.8	23.0 ± 4.0	0.478
HT, n (%)	14 (40.0)	60 (42.9)	0.760
DM, n (%)	4 (11.4)	32 (22.9)	0.135
HL, n (%)	5 (14.3)	21 (15.0)	0.915
CAD, n (%)	0 (0.0)	9 (6.4)	0.207
A. fib, n (%)	1 (2.9)	17 (12.1)	0.129
Prev. stroke/TIA, n (%)	4 (11.4)	22 (15.7)	0.607
Cancer, n (%)	2 (5.7)	17 (12.1)	0.372
GI diseases, n (%)	1 (2.9)	4 (2.9)	1.000
Initial GCS, median (IQR)	13 (9–14)	8 (6-12.75)	< 0.001
F/U GCS, median (IQR)	14 (12–15)	11 (5–13)	< 0.001
Protein balance, mean (SD)*	20.2 ± 23.5	-61.4 ± 39.6	< 0.001
% of IBW	107.4 ± 20.1	109.4 ± 20.4	0.614
Protein, g/kg/day	1.58 ± 0.40	0.58 ± 0.48	< 0.001
Calories, kcal/kg/day	25.6 ± 7.3	11.7 ± 9.5	< 0.001
Diagnosis, n (%)			0.070
IS	1 (2.9)	25 (17.9)	

* Protein balance = nitrogen balance X 6.25

BMI: body mass idex, HT: hypertension, DM: diabeted mellitus, HL: hyperlipidemia, CAD: coronary artery disease, A. fib: atrial fibrillation, TIA: transient ischemic attack, GI: gastrointestinal, GCS: Glasgow Coma Scale, F/U: follow up, IBS: ideal body weight, IS: ischemic stroke, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, ICH: intracerebral hemorrhage, SE: status epilepticus, NPO: nil per os, EN: enteral nutrition, PN: parenteral nutrition, TTM: targeted temperature management, UUN: urine urea nitrogen, IQR: interquartile range, NICU: neurointensive care unit

	Positive nitrogen balance (n = 35, 20.0%)	Negative nitrogen balance (n = 140, 80.0%)	P-value
SAH	9 (25.7)	21 (15.0)	
SDH	2 (5.7)	22 (15.7)	
ICH	10 (28.6)	23 (16.4)	
SE	2 (5.7)	5 (3.6)	
Others	11 (31.4)	44 (31.4)	
Nutrition supplement, n (%)			0.002
NPO	0 (0)	32 (23.0)	
EN	32 (94.1)	101 (75.9)	
PN	2 (5.9)	6 (4.3)	
Managements, n (%)			< 0.001
Coma therapy	0 (0)	8 (5.7)	
TTM	0 (0)	8 (5.7)	
Decompressive surgery	0 (0)	10 (7.1)	
Decompressive surgery with TTM	0 (0.0)	6 (4.3)	
Others	2 (5.7)	35 (25.0)	
Admission to UUN day, median (IQR)	3 (2.0–4.0)	4 (2.0-6.75)	0.065
Neurological worsening, n (%)	2(5.7)	34 (24.3)	0.015
In hospital mortality, n (%)	2 (5.7)	28 (20.0)	0.045
hospital length of stay, median (IQR)	19.0 (12.0–29.0)	28.0 (18.25–49.50)	0.002

* Protein balance = nitrogen balance X 6.25

BMI: body mass idex, HT: hypertension, DM: diabeted mellitus, HL: hyperlipidemia, CAD: coronary artery disease, A. fib: atrial fibrillation, TIA: transient ischemic attack, GI: gastrointestinal, GCS: Glasgow Coma Scale, F/U: follow up, IBS: ideal body weight, IS: ischemic stroke, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, ICH: intracerebral hemorrhage, SE: status epilepticus, NPO: nil per os, EN: enteral nutrition, PN: parenteral nutrition, TTM: targeted temperature management, UUN: urine urea nitrogen, IQR: interquartile range, NICU: neurointensive care unit

	Positive nitrogen balance (n = 35, 20.0%)	Negative nitrogen balance (n = 140, 80.0%)	P-value
NICU length of stay, median (IQR)	4.0 (3.0–11.0)	13.0 (7.0–22.0)	< 0.001
* Protein balance = nitrogen balance X 6.25			
BMI: body mass idex, HT: hypertension, DM: diabeted mellitus, HL: hyperlipidemia, CAD: coronary artery disease, A. fib: atrial fibrillation, TIA: transient ischemic attack, GI: gastrointestinal, GCS: Glasgow Coma Scale, F/U: follow up, IBS: ideal body weight, IS: ischemic stroke, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, ICH: intracerebral hemorrhage, SE: status epilepticus, NPO: nil per os, EN: enteral nutrition, PN: parenteral nutrition, TTM: targeted temperature management, UUN: urine urea nitrogen, IQR: interquartile range, NICU: neurointensive care unit			

Among included patients (n = 175), 77 patients (44.0%) had a follow-up assessment of protein balance on a median NICU day of 10, and 39 patients (50.9%) had an improvement in nitrogen balance. Baseline characteristics and severity of illness on admission were not different between the two groups (Table 2). However, patients who achieved an improvement in nitrogen balance had lesser neurological worsening (15.4% vs. 36.8%, P = 0.032) and lower in-hospital mortality (12.8% vs. 31.6%, P = 0.047), even though initial GCS was comparable to those without improvement in nitrogen balance (Table 2, Fig. 1A and 1B).

Table 2

Clinical characteristics according to improvement of nitrogen balance

	Improvement of nitrogen balance (n = 39, 50.6%)	No improvement of nitrogen balance (n = 38, 49.4%)	P-value
Age, mean (SD), year	62.7 ± 15.1	58.6 ± 17.5	0.273
Male, n (%)	21 (53.8)	20 (52.6)	0.915
BMI, mean (SD), Kg/m2	22.1 ± 4.2	23.0 ± 3.9	0.375
HT, n (%)	16 (41.0)	19 (50.0)	0.429
DM, n (%)	7 (17.9)	11 (28.9)	0.254
HL, n (%)	5 (12.8)	5 (13.2)	1.000
CAD, n (%)	3 (7.7)	2 (5.3)	1.000
A. fib, n (%)	5 (12.8)	5 (13.2)	1.000
Prev. stroke/TIA, n (%)	12 (30.8)	3 (7.9)	0.011
Cancer, n (%)	3 (7.7)	5 (13.2)	0.481
GI diseases, n (%)	1 (2.6)	1 (2.6)	1.000
Initial GCS, median (IQR)	6.0 (5-911)	6.5 (5-11.25)	0.750
F/U GCS, median (IQR)	9.0 (6.0–13.0)	7.0 (3-12.25)	0.075
Nutritional support, n (%)	39 (97.4)	34 (89.5)	0.200
Baseline protein balance, mean (SD), g	-58.3 ± 40.6	-55.7 ± 40.7	0.782
Baseline negative Nitrogen balance, n (%)	36 (92.3)	35 (92.1)	1.000
% of IBW, mean (SD)	105.7 ± 21.3	110.8 ± 21.1	0.289
Bwt loss, n (%)	17 (43.6)	19 (50.0)	0.573
Total I/O, mean (SD)	1742.3 ± 3630.6	1658.8 ± 2384.7	0.906
Negative I/O, n (%)	12 (30.8)	9 (23.7)	0.485

BMI: body mass idex, HT: hypertension, DM: diabeted mellitus, HL: hyperlipidemia, CAD: coronary artery disease, A. fib: atrial fibrillation, TIA: transient ischemic attack, GI: gastrointestinal, GCS: Glasgow Coma Scale, F/U: follow up, IBS: ideal body weight, IS: ischemic stroke, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, ICH: intracerebral hemorrhage, SE: status epilepticus, NPO: nil per os, EN: enteral nutrition, PN: parenteral nutrition, BUN: blood urea nitrogen, AKI: acute kidney injury, TTM: targeted temperature management, UUN: urine urea nitrogen, IQR: interquartile range, NICU: neurointensive care unit

	Improvement of nitrogen balance (n = 39, 50.6%)	No improvement of nitrogen balance (n = 38, 49.4%)	P-value
Diagnosis, n (%)			0.445
IS	10 (25.6)	5 (13.2)	
SAH	10 (25.6)	8 (21.1)	
SDH	6 (15.4)	8 (21.1)	
ICH	6 (15.4)	8 (21.1)	
SE	2 (5.1)	1 (2.6)	
Others	5 (12.8)	11 (28.9)	
Initial Nutrition supplement, n (%)			0.077
NPO	8 (20.5)	13 (34.2)	
EN	27 (69.2)	25 (65.8)	
PN	4 (10.3)	0 (0.0)	
F/U Nutrition supplement, n (%)			0.341
EN	17 (43.6)	23 (60.5)	
PN	3 (7.7)	3 (7.9)	
EN with PN	19 (48.7)	12 (31.6)	
Protein intake on admission (g/kg)	0.66 ± 0.56	0.54 ± 0.48	0.289
Calorie intake on admission (kcal/kg)	12.0 ± 10.1	10.4 ± 9.00	0.455
Protein intake on follow up (g/kg)	1.94 ± 0.63	1.28 ± 0.54	< 0.001
Calorie intake on follow up (kcal/kg)	25.3 ± 7.5	21.5 ± 7.9	0.037

BMI: body mass idex, HT: hypertension, DM: diabeted mellitus, HL: hyperlipidemia, CAD: coronary artery disease, A. fib: atrial fibrillation, TIA: transient ischemic attack, GI: gastrointestinal, GCS: Glasgow Coma Scale, F/U: follow up, IBS: ideal body weight, IS: ischemic stroke, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, ICH: intracerebral hemorrhage, SE: status epilepticus, NPO: nil per os, EN: enteral nutrition, PN: parenteral nutrition, BUN: blood urea nitrogen, AKI: acute kidney injury, TTM: targeted temperature management, UUN: urine urea nitrogen, IQR: interquartile range, NICU: neurointensive care unit

	Improvement of nitrogen balance (n = 39, 50.6%)	No improvement of nitrogen balance (n = 38, 49.4%)	P-value
Initial BUN, mean (SD), mg/dl	16.3 ± 8.3	16.0 ± 10.1	0.885
F/U BUN, mean (SD), mg/dl	23.9 ± 9.6	22.9 ± 11.8	0.692
Event, n (%)			0.348
Coma therapy	2 (5.1)	3 (7.9)	
TTM	2 (5.1)	3 (7.9)	
Decompressive surgery	6 (15.4)	2 (5.3)	
Decompressive surgery with TTM	1 (2.6)	5 (13.2)	
Others	2 (5.1)	3 (7.9)	
Development of AKI, n (%)	3 (7.7)	2 (5.3)	1.000
Neurological deterioration, n (%)	6 (15.4)	14 (36.8)	0.032
In-hospital mortality, n (%)	5 (12.8)	12 (31.6)	0.047
hospital length of stay, median (IQR), day	38.0 (25.0–75.0)	33.5 (23.0-67.25)	0.610
NICU length of stay, median (IQR), day	18.0 (10.0–32.0)	20.50 (13.75–33.25)	0.815

BMI: body mass idex, HT: hypertension, DM: diabeted mellitus, HL: hyperlipidemia, CAD: coronary artery disease, A. fib: atrial fibrillation, TIA: transient ischemic attack, GI: gastrointestinal, GCS: Glasgow Coma Scale, F/U: follow up, IBS: ideal body weight, IS: ischemic stroke, SAH: subarachnoid hemorrhage, SDH: subdural hemorrhage, ICH: intracerebral hemorrhage, SE: status epilepticus, NPO: nil per os, EN: enteral nutrition, PN: parenteral nutrition, BUN: blood urea nitrogen, AKI: acute kidney injury, TTM: targeted temperature management, UUN: urine urea nitrogen, IQR: interquartile range, NICU: neurointensive care unit

Patients with an improved nitrogen balance were administered a higher protein amount (1.94 ± 0.63 g/Kg/day vs. 1.28 ± 0.54 g/Kg/day, P < 0.001) and higher calories (25.3 ± 7.5 Kcal/Kg/day vs. 21.5 ± 7.9 Kcal/Kg/day, P = 0.037) on follow-up than those without improvement in nitrogen balance (Table 2). However, baseline nitrogen balance, weight change, cumulative fluid balance, and routes of nutritional supplementation during the monitoring period were not different between the two groups. Moreover, the risk of new AKI, defined using KDIGO criteria, was similar (7.7% vs. 5.3%, P = 1.00, Fisher's exact test) despite the differences in the amount of protein supplementation between the two groups (Table 2).

Discussion

In this study, we found that a significant proportion of patients were underfed in terms of nitrogen or protein balance, which was associated with poorer outcomes in the NICU. Moreover, an improvement in nitrogen balance with active nutritional support was linked to better neurological outcomes.

A marked increase in protein catabolism has been observed in the acute stage of critical illness, and the types of protein synthesized in the acute phase may differ in patients with severe illness compared to those in healthy conditions, possibly mediated by the intensity of SIR [7, 8, 15, 22, 23]. Conflicting results exist regarding the effect of protein supplementation on outcomes in patients with critical illness. Several studies have shown that a high protein intake during the acute stage of critical illness is associated with lower mortality and fewer complications and can reduce protein breakdown during the catabolic state [5, 10, 24–27]. In contrast, other studies have reported that lower protein intake was better in terms of safety, and fewer complications occurred in general critically ill patients [7, 10, 11, 25, 27, 28].

However, the optimal methods of protein provision have not been determined in neurologically critically ill patients. Therefore, we investigated whether an optimal protein supplementation, assessed by an improvement in nitrogen balance, was associated with better clinical outcomes in patients with severe neurological illnesses. In our study, an improvement in nitrogen balance (zero to positive balance) from basal negative nitrogen balance with adequate provision of protein (mean, 1.94 g/kg/day) was associated with lesser neurological worsening and lower in-hospital mortality. The amount of protein administered to patients with an improvement in nitrogen balance was close to the recommended amount (2.0–2.5 g/kg/day of protein) from the most recent guidelines and expert opinions [9, 15, 29–34]. High protein supplementation may have adverse events including hypertonic dehydration or development of AKI [35], which was not observed in our patients.

Proteins metabolism is shifted to catabolism due to the effect of SIR in patients with critical illness [15, 23, 28]. Stress metabolism is a component of the adaptive response to acute illness and is characterized by over-activation of the ubiquitin-proteasome pathway, which causes excessive protein degradation [7, 8, 15, 22, 23, 28, 36]. In general, a large increase in protein breakdown would lead to an increase in the synthesis of inflammatory mediators. Therefore, a depletion of amino acids essential to the recovery process may lead to an inhibition of protein synthesis and mitochondrial biogenesis and would result in an induction of compensatory energy-recycling responses [37–41]. In contrast, sufficient proteins are activators of anabolic processes that promote cell growth and survival and might promote positive protein balance, decrease inflammation and organ injury, improve immune function, and attenuate tissue damage [38, 42–46]. Hypercatabolism and subsequent insufficient nutritional supplementation can rapidly lead to organ dysfunction and an alteration in the appropriate immune response. Therefore, monitoring nitrogen balance is simple but maybe crucial in evaluating the status of protein degradation [30, 32, 33, 47]. The optimal protein requirement can be defined as the amount required to maintain a neutral tissue protein balance, at least in physiological conditions [36]. We think that these mechanisms

underlying a positive nitrogen balance with optimal protein provision based on serial monitoring may be associated with improvements in neurological outcomes in neurocritically ill patients.

There were several limitations to our study. First, this is a retrospective study, and a certain degree of unmeasured bias can exist. Second, patients with negative nitrogen balance had more severe injuries; thus, a protein underfeeding could be just an epiphenomenon. However, the outcomes were better in patients who showed an improvement in nitrogen balance on follow-up, despite having similar baseline severity. Given the nature of the retrospective observational study, we could not conclude the cause and effect relationship. Therefore, special care should be taken in interpreting the results. Third, UUN may underestimate the total amount of protein catabolism in certain conditions. UUN can only measure nitrogen products excreted in the urine; therefore, if patients are suffering from oliguria or anuria or have non-renal routes of protein loss such as an open abdomen, the estimated nitrogen balance may not be accurate [15]. However, the major population of this study was neurologically ill patients without any condition of open abdomen, and we excluded patients with oliguria. Therefore, we think that UUN measurements played a role in accurately reflecting the state of protein catabolism in our patients. Fourth, we could not measure caloric expenditure using more accurate indirect calorimetry, which could have affected the outcomes [9, 22, 26]. Fifth, micronutrients, such as trace elements and vitamins, were not considered in our study [31–33]. With these limitations, however, we think that our study presents a valid correlation between improving protein balance through adequate protein provision and short-term outcomes in neurocritically ill patients.

Conclusions

In conclusion, this study demonstrated that improving nitrogen balance with optimal protein provision was related to lower in-hospital mortality and better clinical outcomes in NICU patients. This finding suggests that adequate nutrition monitoring and individualized nutrition supplement support should be considered in neurologically ill patients. Further research is needed to confirm the true relationship between optimal protein balance and outcomes with a large number of patients.

Abbreviations

NICU
neurointensive care unit
GCS
Glasgow Coma Scale
SIR
Systemic inflammatory responses
UUN
urine urea nitrogen
BUN
blood urea nitrogen

Cr
creatinine
TTM
targeted temperature management
APACHE
Acute Physiology and Chronic Health Evaluation
EN
enteral nutrition
PN
parenteral nutrition
NPO
nil per os
I
input
O
output
BMI
body mass index
AKI
acute kidney injury
KIDIGO
Kidney Disease:Improving Global Outcomes
SD
standard deviation
IQR
interquartile range

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB Number; IRB NO H-1908-072-1054). The need for informed consent was waived by the IRB.

Consent for publication

All authors have read and approved the submitted manuscript and publication.

Availability of data and materials

Data supporting the findings of this study are available from the corresponding author (Pf. Sang-Bae Ko) on reasonable request.

Competing interests

None.

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Authors' contributions

S-B K. contributed to the study concept and design. JE K., H-S K., WS C. contributed to the study concept. TJ K., S-H P., H-B J., and EJ H. contributed to data collection. TJ K., S-B K. drafted the manuscript and performed data analysis. All authors read and approved the manuscript.

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Disclosure

None.

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Figures

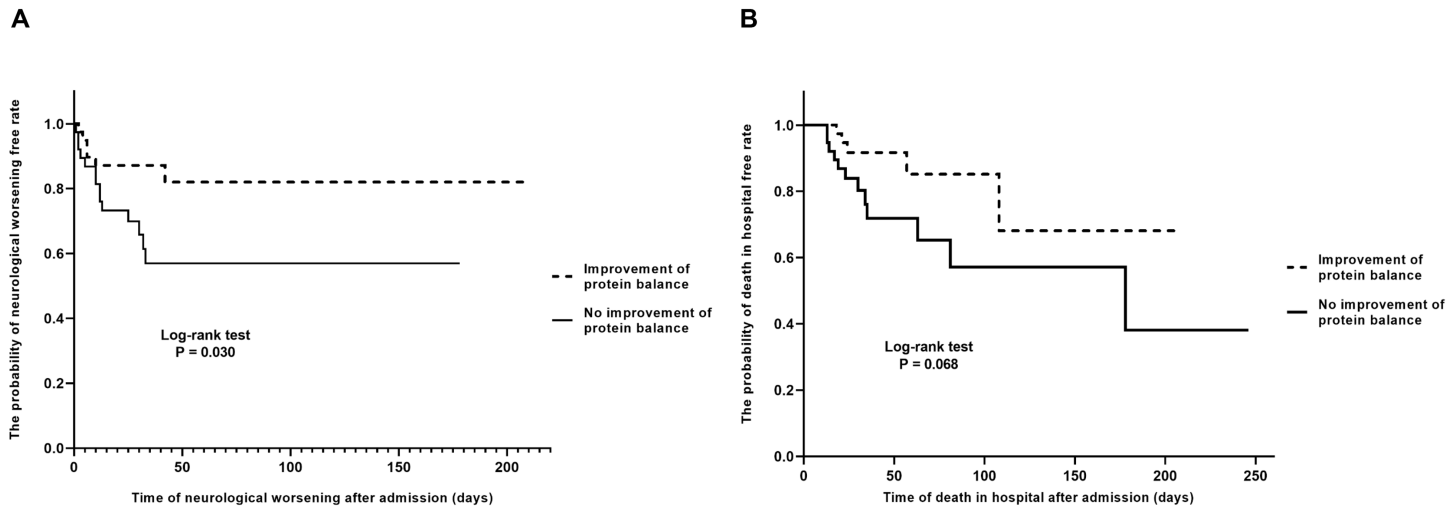

Figure 1

Kaplan-Meier curves for outcomes according to the nitrogen balance Patients with an improvement in protein balance had fewer events of neurological worsening (P = 0.030) (A) and lower in-hospital mortality (P = 0.068) than those without an improvement in protein balance (B).