*Original Article*

# The nitrogen load is affected by high protein provision according to kidney function in critically ill patients

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**Adequate protein delivery is recommended in the acute phase of critical illness with kidney dysfunction. However, the influence of the protein and nitrogen loads has not yet been clarified. Patients admitted to the intensive care unit were included. In the former period, patients received standard care (0.9 g/kg/day protein). In the latter, patients received the intervention of active nutrition therapy with high protein delivery (1.8 g/kg/day protein). Fifty patients in the standard care group and 61 in the intervention group were examined. Maximum blood urea nitrogen (BUN) on days 7–10 were 27.9 (17.3, 38.6) vs 33 (26.3, 51.8) (mg/dl) ($p = 0.031$). The maximum difference in BUN increased [31.3 (22.8, 55) vs 50 (37.3, 75.9) mg/dl ($p = 0.047$)] when patients were limited to an estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m². This difference increased further when patients were limited to eGFR <30 ml/min/1.73 m². No significant differences were observed in maximum Cre or in the use of RRT. In conclusion, the provision of 1.8 g/kg/day protein was associated with an increase in BUN in critically ill patients with kidney dysfunction; however, it was tolerated without the need for RRT.**

*Key Words*:    urea, blood urea nitrogen, creatinine, protein, critical care

T he optimal intake of protein in critical care remains controversial. While protein delivery in the early period of the acute phase[1] may be harmful due to a dysfunction in autophagy,[2] adequate protein delivery in the strategy of permissive underfeeding appears to be necessary and beneficial for physical outcomes.[3,4] Therefore, a high protein delivery of 1.3 g/kg/day[1] or 1.2–2.0 g/kg/day[5] is recommended in the first week of the acute phase by international society guidelines.

This discussion is more complicated in critically ill patients with kidney dysfunction. Although limited information is currently available, these patients often have multiple organ dysfunction, including acute kidney injury, for which adequate protein delivery may be needed to maintain the body composition and immune system.[6] Therefore, it has been recommended that the restriction of protein should not be done for patients with kidney dysfunction, at least to avoid or delay initiating renal replacement therapy (RRT).[7,8] However, the nitrogen load with high protein delivery in the acute phase has been associated with an increase in blood urea nitrogen (BUN), which may necessitate RRT or worsen kidney dysfunction.[9,10] While adequate protein is easily delivered with the immediate removal of BUN when RRT is initiated,[11] protein delivery is often restricted in clinical practice, particularly for patients with kidney dysfunction who are not receiving RRT.[12]

One of the reasons for protein restriction is that the influence of protein delivery and the nitrogen load remain unclear and it has not yet been established whether they are tolerated by patients with kidney dysfunction. A randomized control trial previously demonstrated that the administration of 100 g amino acids in a bolus was safe for kidney function, but with a greater increase in BUN than in the control group.[13] Since a large amount of protein was intravenously delivered in this study and the number of patients with kidney dysfunction before protein delivery was small, the findings obtained lacked sufficient evidence for their application to patients with kidney dysfunction. In another study, a greater increase in BUN was observed in elderly patients provided with high protein enteral nutrition.[10] Therefore, the influence of protein and nitrogen loads on critically ill patients with kidney dysfunction remains unclear.

Herein, we conducted a prospective observational study in which high protein provision with enteral nutrition was compared with medium protein provision. In the present study, the target of 1.8 g/kg/day protein was delivered for 10 intensive care unit (ICU) days to the high protein group. We examined the need for RRT, the prognosis of kidney function, and the trajectory of BUN for 10 days based on kidney function with/without high protein delivery.

## Materials and Methods

**Study design and participants.** The present study was a post-hoc analysis of the Intensive Goal-directed REhabilitation with Electrical muscle stimulation and Nutrition (IGREEN) study.[14] Briefly, IGREEN was a single-center, prospective, and historical control study conducted at Hitachi General Hospital. Patients admitted to the ICU between October 2019 and December 2020 were included. In the former period between October 2019 and February 2020, patients were treated received standard care as a control group. In the latter period between September 2020 and December 2020, patients received active rehabilitation and nutrition therapy with high protein provision, named IGREEN bundles, as an intervention group. Exclusion criteria were as follows: younger than 20 years old, possible pregnancy, anuria, a lower extremity event, such as infection, injury, or amputation, the use of extracorporeal membrane oxygenation, expected to be discharged from the ICU within 2 days, admission to the ICU for a second time during the same hospital stay, and the designation of "do not resuscitate". The IGREEN study was approved by our Ethics Committee (2020-38) and was registered at the University Hospital Medical Information Network-clinical trials registry (UMIN000040290).

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**Intervention.** In the absence of contraindications, enteral nutrition was initiated in both groups via a nasogastric tube within 48 h of admission at 10–20 ml/h with gradual increases. In the standard care group, nutritional therapy was given at the discretion of the attending physician according to the patient's condition and severity. In the intervention group, a nutritional assessment was performed using the malnutrition universal screening tool (MUST)[15] at admission. In the absence of malnutrition (MUST <4), enteral nutrition was gradually increased to 20 kcal/kg/day. In the presence of malnutrition (MUST ≥4), target calorie delivery was set to 30 kcal/kg/day for day 4. After day 7, target calorie delivery for all patients was 30 kcal/kg/day. Target protein delivery was set to 1.8 g/kg/day. Any shortage was compensated for by supplemental parenteral nutrition and intravenous amino acids were also administered. Actual body weight was used for nutritional calculations; however, in the case of body mass index ≥30, body height (m) × body height (m) × 25 was used. Oral nutrition supplements were provided in addition to the hospital diet when patients recovered and were able to take food orally. This intervention was continued until day 10. Details for rehabilitation were previously reported.[14]

**Measurements and outcomes.** We examined differences in BUN and creatinine trajectories and the need for RRT with/without the intervention based on kidney function before the intervention. Maximum BUN on days 7–10 in patients without RRT was assigned as the primary outcome of the present study. The proportion of patients surviving at discharge, the lengths of ICU and hospital stays, the duration of mechanical ventilation, the use of RRT, RRT dependency at discharge, and the Barthel Index and grip strength at hospital discharge (kg) were evaluated as secondary outcomes.

Total calorie and protein deliveries were calculated by a hospital nutritionist. Age, sex, body mass index, sequential organ failure assessment (SOFA) scores, acute physiology and chronic health evaluation (APACHE) II scores, the Charlson comorbidity index, the main diagnosis, and laboratory data, including C reactive protein (CRP), albumin, and the lymphocyte count, were recorded for 10 days. Estimated glomerular filtration rate (eGFR) was calculated as $194 \times (Cre^{-1.094} \times Age^{-0.287})$ for males and $194 \times (Cre^{-1.094} \times Age^{-0.287}) \times 0.739$ for females. The use of adjunctive therapy, such as steroids and continuous neuromuscular blocking agents, was also evaluated.
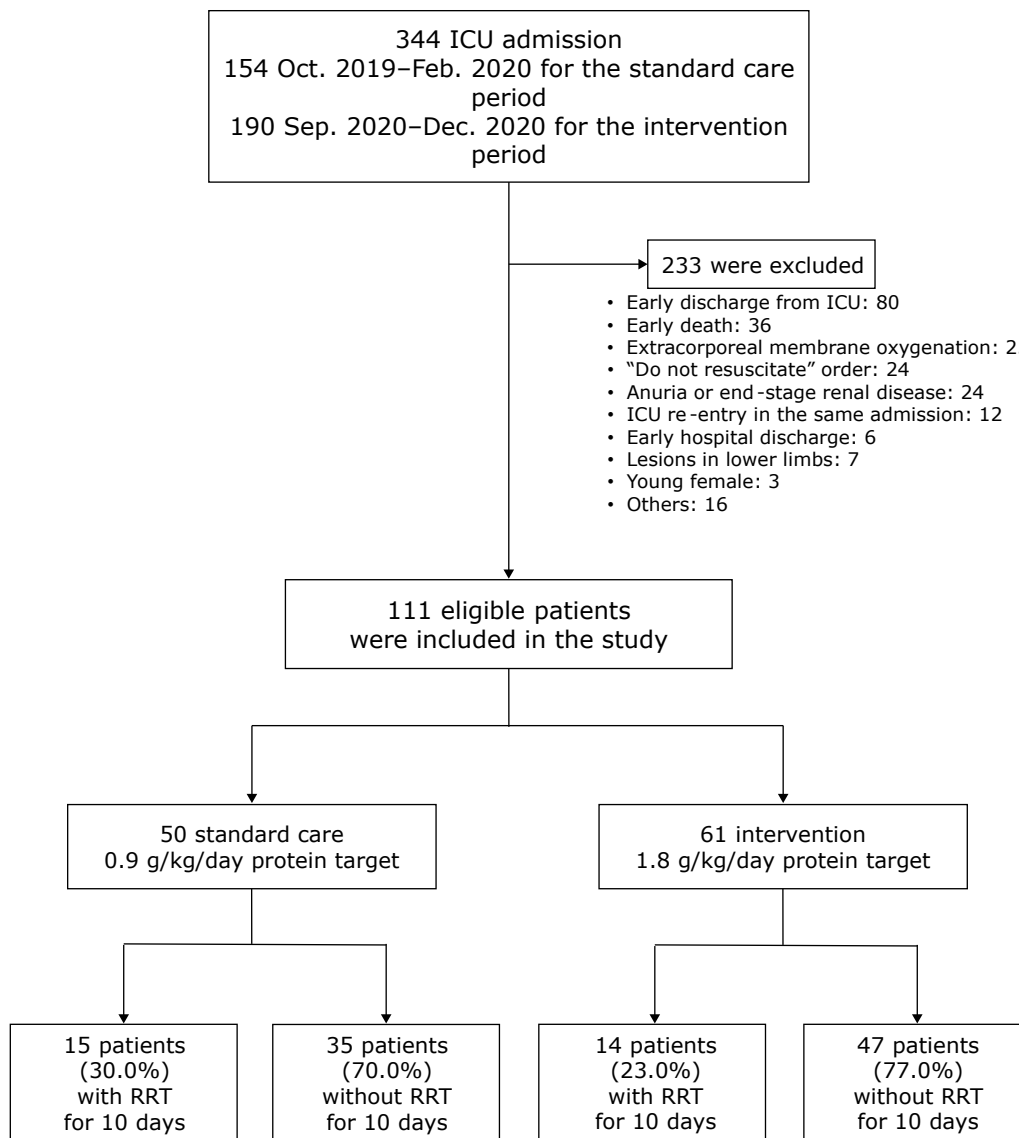


**Fig. 1.** Study outline.

**Statistical analysis.** Results are expressed as the mean ± SD or as a median (interquartile range). Differences were assessed by the application of the *t* test and chi-squared test for normally distributed parameters. The Wilcoxon test was applied for non-normally distributed data. All statistical analyses were conducted using JMP 14 software (SAS Institute Inc., Cary, NC). *P* values <0.05 were considered to be significant.

## Results

The study outline is shown in Fig. 1. A total of 344 patients were admitted to our ICU during the study period. After the exclusion of 233 patients, 50 in the standard care group and 61 in the intervention group were included and intervened for 10 ICU days. Fifteen patients (30.0%) in the standard care group and 14 (23.0%) in the intervention group received RRT for 10 days without an increase in high protein delivery. Standard care was described as 0.9 g/kg/day protein and IGREEN care as 1.8 g/kg/day protein.

The basic characteristics of 111 patients are shown in Table 1. No significant differences were observed in age, sex, body mass index, comorbidity, or APACHEII scores. SOFA scores were higher in the standard care group; 8 (6, 10.25) vs 7 (4, 9) (*p* = 0.048). Diagnoses and adjunctive therapy did not signifi-

**Table 1.** Basic characteristics

| n | Standard care group 50 | Intervention group 61 | p value |
|---|---|---|---|
| Age, years | 71.1 ± 14.6 | 71.6 ± 14.3 | 0.83 |
| Male sex, *n* (%) | 37 (74.0) | 43 (70.5) | 0.68 |
| Body mass index, kg/m$^2$ | 21.7 ± 4.7 | 22.6 ± 4.5 | 0.35 |
| Charlson comorbidity index | 1 (0, 2) | 2 (1, 2) | 0.28 |
| SOFA on admission | 8 (6, 10.25) | 7 (4, 9) | 0.048 |
| APACHE II on admission | 16.5 (12, 22) | 16 (13, 21) | 0.77 |
| Diagnosis, *n* (%) | | | 0.47 |
| Cardiopulmonary arrest | 4 (8.0) | 4 (6.6) | |
| Cardiovascular | 0 (0) | 1 (1.6) | |
| Heart failure | 6 (12.0) | 3 (4.9) | |
| Endocrine and metabolic disorders | 2 (4.0) | 5 (8.2) | |
| GI bleeding | 0 (0) | 1 (1.6) | |
| Post-surgery | 4 (8.0) | 4 (6.6) | |
| Respiratory failure | 2 (4.0) | 6 (9.8) | |
| Sepsis | 21 (42.0) | 27 (44.3) | |
| Stroke | 5 (10.0) | 2 (3.3) | |
| Hematology | 0 (0) | 1 (1.6) | |
| Trauma | 6 (12.0) | 7 (11.5) | |
| Adjunctive treatments | | | |
| Mechanical ventilation, *n* (%) | 38 (76.0) | 47 (77.1) | 0.9 |
| Steroid, *n* (%) | 24 (39.3) | 23 (46.0) | 0.48 |
| Neuromuscular blocking agent, *n* (%) | 0 (0) | 1 (1.6) | 0.72 |
| Cre on day 1, mg/dl | 1.195 (0.75, 1.88) | 1.02 (0.78, 1.72) | 0.54 |
| eGFR on day 1, ml/min/1.73 m$^2$ | 46.0 (28.5, 73.3) | 51.0 (30.25, 73.0) | 0.64 |

**Table 2.** Energy delivery and outcomes

| n | Standard care group 50 | Intervention group 61 | p value |
|---|---|---|---|
| Average energy delivery on days 1–3, kcal/kg/day | 10.3 (6.3, 14.3) | 14.5 (12.2, 17.9) | <0.0001 |
| Average protein delivery on days 1–3, g/kg/day | 0.46 (0.29, 0.68) | 1.08 (0.88, 1.33) | <0.0001 |
| Average energy delivery on days 4–7, kcal/kg/day | 18.2 (12.1, 23.5) | 21.8 (17.6, 25.2) | 0.032 |
| Average protein delivery on days 4–7, g/kg/day | 0.78 (0.53, 1.20) | 1.67 (1.31, 1.83) | <0.0001 |
| Average energy delivery on days 8–10, kcal/kg/day | 18.7 (14.4, 24.6) | 20.3 (14.2, 27.7) | 0.2 |
| Average protein delivery on days 8–10, g/kg/day | 0.87 (0.57, 1.12) | 1.43 (0.86, 1.72) | 0.0013 |
| RRT use on day 10, *n* (%) | 4 (8.0) | 2 (3.3) | 0.27 |
| RRT dependency at discharge, *n* (%) | 0 (0) | 0 (0) | 0 |
| In-hospital mortality, *n* (%) | 9 (18.0) | 7 (11.5) | 0.33 |
| Length of hospital stay, day | 23.5 (15.75, 36) | 28 (13, 52.5) | 0.74 |
| Length of ICU stay, day | 5 (4, 8.25) | 6 (4, 9.5) | 0.53 |
| Duration of mechanical ventilation, day | 2.5 (0.75, 5.25) | 3 (1, 5.5) | 0.48 |
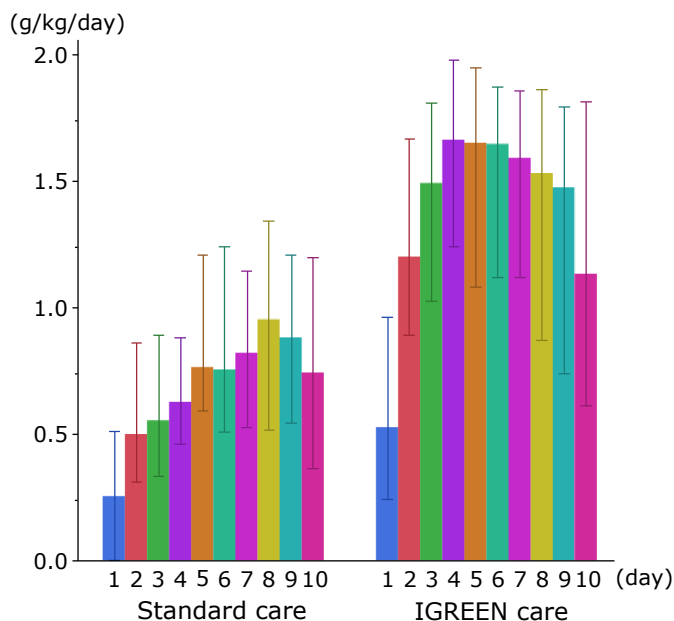
(g/kg/day)

**Fig. 2.** Trajectory of protein delivery through days 1–10. Each bar represents the median of protein (g/kg/day) delivered with error bars of the interquartile range.

cantly differ. Creatinine and eGFR on admission were also not significantly different in both groups.

The trajectory of nutrition therapy in both groups is shown in Table 2 and Fig. 2. Table 2 shows the medians of energy and protein deliveries on days 1–3, 4–7, and 8–10. Energy and protein deliveries were both high in the intervention group throughout the intervention period. Figure 2 shows protein delivery (g/kg/day) each day. Medians of approximately 0.8 g/kg/day protein in the standard care group and 1.6 g/kg/day protein in the intervention group were delivered. Regarding outcomes in both groups, RRT was used on day 10 for 4 (8.0%) vs 2 (3.3%) ($p = 0.27$). RRT dependency at discharge was not observed in any patients in either group. In-hospital mortality, the lengths of hospital and ICU stays, and the duration of mechanical ventilation did not significantly differ between the groups.

A comparison of outcomes, including BUN and creatinine trajectories, without the use of RRT is shown in Table 3 and Fig. 3. Maximum BUN on days 7–10 was 27.9 (17.3, 38.6) vs 33 (26.3, 51.8) (mg/dl) in the patients not requiring renal replacement therapy through days 1–10, with a significant difference ($p = 0.031$). However, the median was not high at 33 mg/dl and maximum Cre on days 7–10 (mg/dl) was not significantly different. The trajectory of BUN was slightly higher (Fig. 3A). However, the maximum difference in BUN increased [31.3 (22.8, 55) vs 50 (37.3, 75.9) mg/dl ($p = 0.047$)] when patients were limited to eGFR <50 ml/min/1.73 m² (Table 3). It increased further [49.7 (29.3, 55) vs 87.5 (63.3, 160.4) mg/dl ($p = 0.033$)] when patients were limited to eGFR <30 ml/min/1.73 m². The difference in the trajectory of BUN was also markedly higher between the groups (Fig. 3B and C). It is important to note that there was no significant difference in maximum Cre on days 7–10 or in the use of RRT. Other outcomes were also similar between the groups.

## Discussion

A high protein delivery strategy (target of 1.8 g/kg/day protein) was safely performed without an increase in the need for RRT. Marked increases in BUN were observed in patients with kidney dysfunction, but were tolerated because the influence on creatine was low and it did not affect the use of RRT.

The safety of high protein delivery to critically ill patients has already been demonstrated.[13] An increase in BUN was also reported;[10] however, the influence of this increase in patients with kidney dysfunction remains unclear. To the best of our knowledge, this is the first study to analyze BUN/creatinine trajectories and the use of RRT with high protein delivery based on kidney function. We found that enteral protein delivery of 1.8 g/kg/day was tolerated even by patients with kidney dysfunction. Although BUN increased after protein delivery, it did not result in adverse events, such as a change in the prognosis of kidney function itself. Therefore, attempts need to be made to delivery adequate amounts of protein to critically ill patients with kidney dysfunction.

The amount of protein recommended for delivery to patients with kidney dysfunction in clinical practice has not yet been established. The protein requirement varies widely and is difficult to estimate precisely, even in healthy individuals.[16] The American Society for Clinical Nutrition and Metabolism recom-

**Table 3.** Outcomes by estimated glomerular filtration rate

| | Overall | | | eGFR <50 ml/min/1.73 m² | | | eGFR <30 ml/min/1.73 m² | | |
|---|---|---|---|---|---|---|---|---|---|
| | Standard care group | Intervention group | *p* value | Standard care group | Intervention group | *p* value | Standard care group | Intervention group | *p* value |
| *n* | 35 | 47 | | 21 | 18 | | 9 | 5 | |
| maximum BUN on days 7–10, mg/dl | 27.9 (17.3, 38.6) | 33 (26.3, 51.8) | 0.031 | 31.3 (22.8, 55) | 50 (37.3, 75.9) | 0.047 | 49.7 (29.3, 55) | 87.5 (63.3, 160.4) | 0.033 |
| maximum Cre on days 7–10, mg/dl | 0.79 (0.55, 1.21) | 0.85 (0.69, 1.18) | 0.37 | 1.03 (0.82, 1.76) | 1.21 (0.90, 1.91) | 0.46 | 1.65 (1, 1.81) | 2.54 (1.59, 2.88) | 0.062 |
| RRT dependency at discharge, *n* (%) | 0 (0) | 0 (0) | 0 | 0 (0) | 0 (0) | 0 | 0 (0) | 0 (0) | 0 |
| In-hospital mortality, *n* (%) | 5 (14.3) | 5 (10.6) | 0.62 | 2 (9.5) | 4 (22.2) | 0.27 | 0 (0) | 3 (60.0) | 0.0052 |
| Length of hospital stay, day | 21 (15, 40) | 28 (12.5, 56) | 0.59 | 20 (15, 26.5) | 44 (15.5, 70) | 0.12 | 18 (14.5, 25.5) | 26 (11, 64.5) | 0.84 |
| Length of ICU stay, day | 5 (4, 8) | 6 (4, 9) | 0.44 | 5 (3.5, 7.5) | 7 (4, 10.25) | 0.16 | 5 (3.5, 8.5) | 6 (3.5, 10) | 0.69 |
| Duration of mechanical ventilation, day | 2 (1, 4) | 3 (1, 5) | 0.31 | 2 (0, 3.5) | 4 (0, 7.25) | 0.28 | 1 (0, 4) | 1 (0, 7) | 0.89 |
| Barthel Index at hospital discharge | 75 (7.5, 100) | 50 (5, 90) | 0.28 | 75 (15, 100) | 30 (0, 92.5) | 0.12 | 75 (32.5, 100) | 0 (0, 82.5) | 0.069 |
| Grip strength at hospital discharge, kg | 19 (0, 25) | 14.5 (0, 21.8) | 0.58 | 21 (2, 30) | 15.5 (3.2, 21.2) | 0.26 | 21 (6, 29) | 14.5 (0, 23.2) | 0.31 |
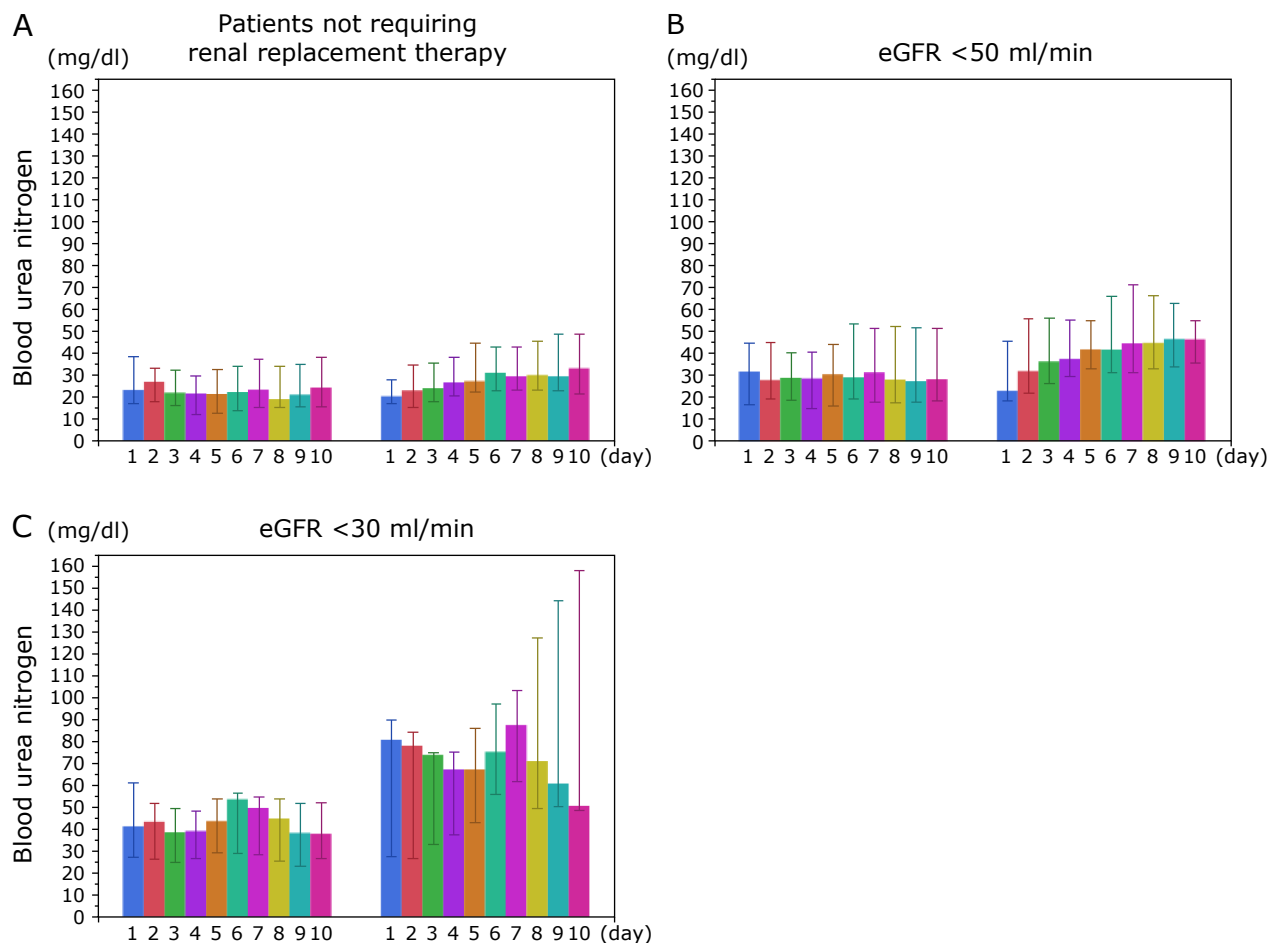
**Fig. 3.** Blood urea nitrogen trajectory through days 1–10. (A) Patients not requiring renal replacement therapy through days 1–10. (B) Patients with eGFR <50 ml/min (without renal replacement therapy through days 1–10). (C) Patients with eGFR <30 ml/min (without renal replacement therapy through days 1–10). Each bar represents the median of blood urea nitrogen (mg/dl) with error bars of the interquartile range. eGFR, estimated glomerular filtration rate.

mend 1.2–2.0 g/kg protein, which is similar to that for other critical care nutrition.[7] On the other hand, in their guidelines for patients with kidney diseases, the European Society for Clinical Nutrition and Metabolism recommends slight changes in the protein target based on the condition of a patient.[8] Regarding patients with kidney diseases hospitalized for acute critical illnesses, they recommended the initiation of 1 g/kg/day protein with a gradual increase to 1.3 g/kg. Since critically ill patients often have a negative nitrogen balance due to a catabolic state and kidney dysfunction also affects the renal excretion of nitrogen, BUN easily increases.[6] However, increased protein delivery may limit nitrogen losses, even in patients with kidney dysfunction.[11,17,18]

Based on the present results, an enteral protein target of 1.8 g/kg/day may be well tolerated by ICU patients with kidney dysfunction. RRT was introduced for some patients; however, the intervention was not associated with the frequency of use of RRT. A previous study reported that 1.5 g/kg/day protein was needed based on the findings of a nitrogen balance analysis of patients with acute kidney injury.[19] To maintain a high delivery of protein, the active introduction of intravenous amino acids is recommended, even for patients with kidney dysfunction.[20] The delivery of a large amount of protein may be achieved with the combination of enteral nutrition and intravenous amino acids, and may be safely administered to critically ill patients with kidney dysfunction.

The present study had several limitations. This was a single-center historical control study; therefore, selection bias cannot be excluded. A multicenter randomized controlled study is needed for a more accurate evaluation. Although no significant differences were observed in demographic characteristics, the number of patients admitted to the ICU differed due to the difference in time periods between the standard care and intervention groups, which resulted in different numbers of patients being analyzed. As we excluded the patients with anuria, patients with severe kidney dysfunction or complete renal failure could not be included into this study. Nutrition therapy after the initiation of oral intake was inadequate. Another limitation is that the effects of treatment after day 10 were not assessed and may have affected the outcomes. It is also important to analyze nutrition therapy during the recovery period in the future. In addition, the long-term prognosis of patients was not evaluated in the present study.

The provision of 1.8 g/kg/day protein was associated with increases in BUN in critically ill patients with kidney dysfunction; however, this was tolerated without the need for RRT.

## Author Contributions

MM: interpretation and drafting of the manuscript. HH: data curation. MM, HN, DI, YT, and HH: conduction of the study. KN: conception of the study, data analysis, revision of the

manuscript and supervision of the study. All authors have read and approved the manuscript.

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## Abbreviations

| | |
|---|---|
| APACHE | acute physiology and chronic health evaluation |
| eGFR | estimated glomerular filtration rate |
| ICU | intensive care unit |
| SOFA | sequential organ failure assessment |

## Conflict of Interest

No potential conflicts of interest were disclosed.

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