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Impact of Intradialytic Renal Rehabilitation on the Urea Nitrogen-to-Creatinine Ratio and Its Association With Mortality in Patients on Maintenance Hemodialysis: A Post Hoc Analysis of a Nationwide Multicenter Retrospective Cohort Study (REVEAL-D)

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Abstract

Background: The urea nitrogen-to-creatinine (UN/Cre) ratio has been associated with adverse outcomes in patients undergoing hemodialysis (HD) and may reflect nutritional and catabolic status. We primarily investigated whether intradialytic renal rehabilitation was associated with longitudinal changes in the UN/Cre ratio and additionally examined its prognostic significance and associations with clinical parameters.

Methods: This was a post hoc analysis of the REVEAL-D retrospective study, a nationwide multicenter cohort in Japan of patients undergoing maintenance HD. The UN/Cre ratio and intradialytic renal rehabilitation status were assessed annually from 2021 to 2024. Linear mixed-effects models were used to evaluate longitudinal changes in the log-transformed UN/Cre ratio according to renal rehabilitation status. Associations of the baseline UN/Cre ratio with all-cause mortality and hospitalization were assessed using multivariable Cox proportional hazards models, and its associations with clinical parameters using multivariable linear regression analysis.

Results: A total of 695 patients were included; 224 (32%) were receiving renal rehabilitation at baseline. The interaction between renal rehabilitation and study period was not significantly associated with longitudinal changes in the log-transformed UN/Cre ratio, whether rehabilitation status was defined at baseline or treated as a time-varying variable. During a median follow-up of 36 months, 142 patients (20%) died. A higher log-transformed UN/Cre ratio was independently associated with all-cause mortality after full adjustment, including renal rehabilitation status and clinical frailty (hazard ratio, 1.82; 95% confidence interval, 1.02–3.24; P = 0.04), but not with all-cause hospitalization. Higher UN/Cre ratios were also associated with older age, female sex, greater frailty,

diabetes mellitus, lower systolic blood pressure, lower albumin and hemoglobin levels, and higher log-transformed C-reactive protein levels. Of the factors independently associated with a higher UN/Cre ratio, hemoglobin level was the only potentially modifiable factor.

Conclusions: In this Japanese cohort of patients undergoing maintenance HD, intradialytic renal rehabilitation was not associated with longitudinal changes in the UN/Cre ratio. Although a higher UN/Cre ratio was independently associated with all-cause mortality and may reflect the complex interplay of nutritional, inflammatory, and other physiological factors, its clinical utility as a modifiable treatment target remains uncertain.

Keywords: hemodialysis; urea nitrogen-to-creatinine ratio; renal rehabilitation; mortality; hospitalization

Introduction

The urea nitrogen-to-creatinine (UN/Cre) ratio is a readily available metric that can be calculated from routinely measured laboratory parameters in patients undergoing hemodialysis (HD). The UN/Cre ratio reflects multiple pathophysiological processes, including reduced renal perfusion, neurohormonal activation, increased protein catabolism, and volume depletion. An elevated UN/Cre ratio has been associated with adverse clinical outcomes and has been proposed as a potential prognostic marker in various clinical conditions, including acute kidney injury, heart failure, acute myocardial infarction, and acute ischemic stroke.[1–4] In patients undergoing HD, the UN/Cre ratio may reflect not only dietary protein intake but also catabolic stress, including protein-energy wasting (PEW) and inflammation. Recent studies, primarily from Japan, have reported that an elevated UN/Cre ratio is associated with poorer clinical outcomes in patients undergoing maintenance HD.[5,6]

Intradialytic exercise therapy may represent a potentially modifiable factor that could influence the UN/Cre ratio. Exercise performed during HD may attenuate catabolic processes, preserve or improve skeletal muscle mass, and potentially enhance the removal of uremic solutes through increased muscle perfusion and dialysis efficiency. These effects may, in turn, contribute to a reduction in the UN/Cre ratio. Supporting this hypothesis, a small randomized controlled trial demonstrated that 8 weeks of intradialytic exercise therapy significantly reduced the UN/Cre ratio in patients undergoing HD.[7] However, whether intradialytic exercise therapy is associated with longitudinal changes in the UN/Cre ratio in a larger and more representative population remains unclear.

Recently, we reported the results of the Registry of Active Renal Rehabilitation in Dialysis Patients (REVEAL-D), a nationwide multicenter retrospective cohort study conducted in Japan, demonstrating a favorable association between intradialytic renal rehabilitation, defined as supervised intradialytic exercise instruction plus nutritional and lifestyle guidance (≥1 session/week for ≥1 month), and mortality among patients undergoing maintenance HD.[8] These findings raise the possibility that the UN/Cre ratio, which may reflect nutritional and catabolic status, could be a modifiable physiological marker associated with intradialytic renal rehabilitation and clinical outcomes.

Therefore, as a post hoc analysis of the REVEAL-D study, the present study aimed to examine the longitudinal association between intradialytic renal rehabilitation and changes in the UN/Cre ratio in patients undergoing maintenance HD. We additionally investigated the prognostic significance of the UN/Cre ratio for mortality and examined whether this association was independent of intradialytic renal rehabilitation.

Methods

Study Design and Population

The REVEAL-D study comprises two components: a prospective cohort and a retrospective cohort study. The present study was a post hoc analysis of the retrospective cohort, referred to as the REVEAL-D retro study, which was reviewed and approved by the Ethics Committee of Tokyo Women's Medical University (approval number: 2023-0204). The study was conducted in accordance with the principles of the Declaration of Helsinki. The detailed study protocol has been described previously.[9] Briefly, adult patients undergoing outpatient HD were recruited from 10 dialysis facilities across Japan

between January 2021 and January 2024. An opt-out opportunity was provided, and patients who opted out were excluded from the study. Patients were considered to be undergoing renal rehabilitation if they received intradialytic exercise instruction at least once per week for at least 1 month following study enrollment. In addition to exercise, renal rehabilitation encompassed periodic nutritional and lifestyle counseling from physicians, nurses, dietitians, physical therapists, or clinical engineers. Patients were also required to have at least 6 months of follow-up. In the primary analysis, a total of 708 patients were included, of whom 228 were undergoing renal rehabilitation and 480 were not.[8] In the present analysis, because the UN/Cre ratio was the key variable of interest, patients with missing UN/Cre ratio data were excluded.

Primary and Secondary Outcome Measures

The primary analysis evaluated the association between intradialytic renal rehabilitation and longitudinal changes in the UN/Cre ratio. The UN/Cre ratio was measured annually from study enrollment, for a maximum of four measurements: January 2021, January 2022, January 2023, and January 2024.

For the primary analysis, renal rehabilitation status was defined in two ways as a fixed effect. First, renal rehabilitation status at study enrollment (January 2021) was used to define the renal rehabilitation and non-rehabilitation groups, corresponding to the group classification used in the REVEAL-D primary analysis. Second, participation in renal rehabilitation was assessed annually at each measurement time point (January 2021, January 2022, January 2023, and January 2024).

As a secondary analysis, the association between the UN/Cre ratio at study enrollment (January 2021) and mortality or hospitalization was evaluated using multivariable survival analyses. Other baseline parameters were selected as covariates according to the REVEAL-D primary analysis.[8] Additionally, associations between the UN/Cre ratio and other clinical and physiological parameters were assessed to further characterize what the UN/Cre ratio represents clinically and physiologically.

Statistical Analysis

For the primary analysis, linear mixed models were used to assess the association between renal rehabilitation and longitudinal changes in the UN/Cre ratio. The log-transformed UN/Cre ratio was used as the dependent variable because of its severe right-skewness. The models included renal rehabilitation status, period (January 2021, January 2022, January 2023, and January 2024), sex, and baseline age (years), dialysis vintage (years), clinical frailty, serum albumin (g/dL), and C-reactive protein (CRP, mg/L) levels as fixed effects. Clinical frailty was categorized into three groups according to the Clinical Frailty Scale (CFS) score, as previously described.[8] These covariates were selected based on analyses from a previous study that identified factors associated with the UN/Cre ratio in patients undergoing HD and from the main REVEAL-D retro study.[5,8] An interaction term between renal rehabilitation status and period was also included as a fixed effect to evaluate the longitudinal association between renal rehabilitation and changes in the UN/Cre ratio. As described above, renal rehabilitation status was assessed in two ways: Model 1, based on renal rehabilitation status at study enrollment; and Model 2, based on

renal rehabilitation status at each measurement time point, treated as a time-varying variable (January 2021, January 2022, January 2023, and January 2024).

As a secondary analysis, the associations between the UN/Cre ratio and all-cause mortality and all-cause hospitalization were assessed using survival analyses. Univariable Cox proportional hazards models were first used to evaluate the crude associations, followed by multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for these outcomes. Covariates were selected based on the survival analyses in the main REVEAL-D retro study and included age, sex, dialysis vintage, clinical frailty, diabetes, history of cardiovascular disease, smoking, and renal rehabilitation status at baseline (Model 1). Model 2 additionally included baseline systolic blood pressure (mmHg), serum albumin, hemoglobin (g/dL), CRP, use of renin–angiotensin system inhibitors, and use of statins.

Additionally, associations between the UN/Cre ratio and the clinical parameters included in the survival analyses were assessed. For continuous variables, Pearson correlation analysis was used to assess the associations with the log-transformed UN/Cre ratio. For binary variables, the log-transformed UN/Cre ratio was compared between groups using the unpaired t-test. For categorical variables with three groups, one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons was used to compare the log-transformed UN/Cre ratio across groups.

Multiple linear regression analyses were additionally performed to assess the independent associations between the UN/Cre ratio and other clinical parameters. The log-transformed UN/Cre ratio was used as the dependent variable, and the same covariates as those used in the above models (Models 1 and 2) were included as

independent variables. Because CRP was severely right-skewed, it was log-transformed before inclusion in the statistical models. The UN/Cre ratio was also log-transformed before inclusion in all statistical models, as described above.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, ver. 32; IBM Corp., NY, USA), with a p-value <0.05 considered statistically significant.

Results

Patient Flow and Baseline Characteristics

Among 708 patients (228 on renal rehabilitation and 480 not on renal rehabilitation at baseline), 13 patients were excluded because UN/Cre ratio were not calculated due to missing value of both serum UN and creatinine (n =12) or solely UN value (n = 1): consequently, 695 patients were included in this post hoc analysis (Figure 1).

Table 1 summarizes the baseline clinical characteristics of the study participants, and longitudinal data regarding continued participation in renal rehabilitation. Median UN/Cre ratio was 6.5, while mean log-transformed UN/Cre ratio was 1.88. Although 224 patients (32%) were on renal rehabilitation at baseline, while the proportion decreases longitudinally, with 184 (26%) on January 2022, 139 (20%) on January 2023, and 88 (13%) on January 2024.

Table 1. Baseline clinical characteristics and longitudinal participation in renal rehabilitation among the study participants

Variables	All (*n* = 695)
Age (years)	69.9 ± 11.1
Gender (% male)	412 (59%)
Dialysis vintage (years)	6 (2–11)
Diabetes mellitus (%)	287 (41%)
CVD history (%)	274 (39%)
Smoking (%)	190 (27%)
RAS inhibitor use (%)	284 (41%)
Statin use (%)	247 (36%)
Modality (%HDF)	386 (56%)
Clinical frailty scale	
Non-frail (%)	314 (45%)
Mild (%)	178 (26%)
Severe (%)	75 (11%)
Renal rehabilitation	
Baseline (January 2021, %)	224 (32%)
January 2022 (%)	184 (26%)
January 2023 (%)	139 (20%)
January 2024 (%)	88 (13%)
BMI (kg/m^2)	21.9 ± 4.2
Systolic blood pressure (mmHg)	149.2 ± 22.4
Diastolic blood pressure (mmHg)	77.9 ± 13.5
Albumin (g/dL)	3.5 ± 0.4
Hemoglobin (g/dL)	11.2 ± 1.1
Urea nitrogen (mg/dL)	60.0 ± 15.6
Creatinine (mg/dL)	9.2 ± 2.6
UN/Cre ratio	6.5 (5.3–7.8)

Log-transformed UN/Cre ratio	1.88 ± 0.30
Calcium (mg/dL)	8.6 ± 0.6
Phosphorus (mg/dL)	5.3 ± 1.4
PTH (pg/mL)	125 (74–205)
Kt/V	1.59 ± 0.34
C-reactive protein (mg/L)	1.6 (0.7–4.1)
Log-transformed C-reactive protein (mg/L)	0.56 ± 1.40

Abbreviations: CVD, cardiovascular disease; RAS, renin-angiotensin system; HDF, hemodiafiltration; BMI, body mass index; UN/Cre ratio, urea nitrogen-to-creatinine ratio; PTH, parathyroid hormone.

Effect of Renal Rehabilitation on Longitudinal Changes in the UN/Cre Ratio

In the linear mixed model with baseline renal rehabilitation status as a fixed effect (Model 1), the log-transformed UN/Cre ratio changed from 1.86 ± 0.03 at baseline (January 2021) to 1.81 ± 0.03 in January 2022, 1.77 ± 0.03 in January 2023, and 1.84 ± 0.03 in January 2024 in the rehabilitation group. In the non-rehabilitation group, the corresponding values were 1.84 ± 0.02, 1.82 ± 0.02, 1.81 ± 0.02, and 1.80 ± 0.02, respectively (Figure 2A). The interaction between renal rehabilitation status and period was not statistically significant.

When longitudinal renal rehabilitation status was included as a fixed effect (Model 2), the log-transformed UN/Cre ratio changed from 1.85 ± 0.03 at baseline (January 2021) to 1.79 ± 0.03 in January 2022, 1.76 ± 0.03 in January 2023, and 1.86 ± 0.03 in January 2024 in the rehabilitation group. In the non-rehabilitation group, the corresponding values were 1.85 ± 0.02, 1.82 ± 0.02, 1.80 ± 0.02, and 1.80 ± 0.02, respectively (Figure 2B). The interaction between renal rehabilitation status and period was also not statistically significant in Model 2.

Survival Analysis: Association Between the UN/Cre Ratio and Outcomes

During a median follow-up of 36 (interquartile range, 32–36) months, 142 patients (20%) died. In the univariable Cox proportional hazards model, a higher log-transformed UN/Cre ratio was significantly associated with a higher risk of all-cause mortality (Table 2; HR, 4.20; 95% CI, 2.59–6.82; P < 0.001). In multivariable Cox proportional hazards analysis, the log-transformed UN/Cre ratio remained significantly associated with all-cause mortality in Model 1 (HR, 1.82; 95% CI, 1.07–3.07; P = 0.03) and Model 2 (HR, 1.82; 95% CI, 1.02–3.24; P = 0.04).

During the study period, 455 patients (65%) experienced all-cause hospitalization, and the median time to first hospitalization was 20 (interquartile range, 8–36) months. In the crude analysis, a higher log-transformed UN/Cre ratio was significantly associated with all-cause hospitalization (Table 2; HR, 1.61; 95% CI, 1.20–2.16; P = 0.001). However, the association was no longer statistically significant after multivariable adjustment in either Model 1 (HR, 0.95; 95% CI, 0.66–1.36; P = 0.78) or Model 2 (HR, 0.84; 95% CI, 0.56–1.25; P = 0.38).

Table 2. Association between log-transformed UN/Cre ratio and all-cause mortality or all-cause hospitalization in patients undergoing hemodialysis using Cox proportional hazard model

	All-cause mortality		All-cause hospitalization	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Crude	4.20 (2.59–6.82)	<0.001	1.61 (1.20–2.16)	0.001
Model 1	1.82 (1.07–3.07)	0.03	0.95 (0.66–1.36)	0.78
Model 2	1.82 (1.02–3.24)	0.04	0.84 (0.56–1.25)	0.38

Model 1 was a minimally adjusted model with age, sex, dialysis vintage, clinical frailty, diabetes, history of cardiovascular disease, smoking, and renal rehabilitation status at baseline. Model 2 additionally included baseline systolic blood pressure (mmHg), serum albumin (g/dL), hemoglobin (g/dL), log-transformed C-reactive protein (mg/L), use of renin–angiotensin system inhibitors, and use of statins.

Abbreviations: UN/Cre ratio, urea nitrogen-to-creatinine ratio; HR, hazard ratio; CI, confidence interval.

Clinical Parameters Associated with the UN/Cre Ratio

The mean log-transformed UN/Cre ratio was significantly higher in female than in male patients (1.98 ± 0.29 vs. 1.82 ± 0.29, P < 0.001). It was also significantly higher in patients with diabetes mellitus (DM) than in those without DM and in nonsmokers than in smokers (1.92 ± 0.29 vs. 1.86 ± 0.30, P = 0.006; 1.90 ± 0.31 vs. 1.82 ± 0.27, P = 0.002, respectively). The log-transformed UN/Cre ratio was numerically higher in patients with a history of cardiovascular disease (CVD) than in those without a history of CVD, although the difference was not statistically significant (1.91 ± 0.30 vs. 1.87 ± 0.29, P = 0.08). There was also no significant difference between patients with and without renal rehabilitation at baseline (1.89 ± 0.28 vs. 1.88 ± 0.31, P = 0.65). Similarly, no significant differences were observed between users and nonusers of renin–angiotensin system inhibitors or statins (1.87 ± 0.29 vs. 1.89 ± 0.30, P = 0.41; 1.85 ± 0.28 vs. 1.90 ± 0.30, P = 0.06, respectively).

The mean log-transformed UN/Cre ratio differed significantly across the three frailty categories, with values of 1.84 ± 0.26, 1.91 ± 0.29, and 2.02 ± 0.37 in non-frail, mildly frail, and severely frail patients, respectively (P < 0.001). In the post hoc analysis with Bonferroni correction, the ratio was significantly higher in severely frail patients than in both non-frail and mildly frail patients (P < 0.001 and P = 0.01, respectively), and was also significantly higher in mildly frail patients than in non-frail patients (P = 0.02).

Among continuous clinical variables, age and log-transformed CRP were significantly positively correlated with the log-transformed UN/Cre ratio (r = 0.34, 95% CI, 0.27–0.40, P < 0.001; r = 0.10, 95% CI, 0.03–0.18, P = 0.009, respectively). In contrast, systolic blood pressure, serum albumin, and hemoglobin were significantly

negatively correlated with the log-transformed UN/Cre ratio (r = −0.09, 95% CI, −0.17 to −0.02, P = 0.01; r = −0.13, 95% CI, −0.20 to −0.06, P < 0.001; and r = −0.13, 95% CI, −0.20 to −0.06, P < 0.001, respectively) (Table 3).

In multivariable linear regression analysis (Model 1), age was significantly positively associated with the log-transformed UN/Cre ratio (β = 0.008, 95% CI, 0.005–0.010, P < 0.001) (Table 4). Female sex and the presence of DM were also significantly associated with higher log-transformed UN/Cre ratios (β = 0.16, 95% CI, 0.11–0.21, P < 0.001; β = 0.06, 95% CI, 0.01–0.11, P = 0.01, respectively). In Model 2, age remained significantly positively associated with the log-transformed UN/Cre ratio (β = 0.008, 95% CI, 0.005–0.010, P < 0.001), and female sex and the presence of DM remained significantly associated with higher log-transformed UN/Cre ratios (β = 0.16, 95% CI, 0.11–0.21, P < 0.001; β = 0.08, 95% CI, 0.03–0.14, P = 0.001, respectively). Additionally, higher hemoglobin levels were significantly associated with a lower log-transformed UN/Cre ratio (β = −0.03, 95% CI, −0.05 to −0.01, P = 0.01).

Table 3 Correlations of clinical parameters with log-transformed UN/Cre ratio

	Log-transformed Un/Cre ratio		
Variable	***r***	**95% CI**	***P* value**
Age (year)	0.34	0.27–0.40	<0.001
Dialysis vintage (years)	−0.06	−0.14–0.01	0.09
Systolic blood pressure (mmHg)	−0.09	−0.17 to −0.02	0.01
Albumin (g/dL)	−0.13	−0.20 to −0.06	<0.001
Hemoglobin (g/dL)	−0.13	−0.20 to −0.06	<0.001
Log-transformed C-reactive protein (mg/L)	0.10	0.03–0.18	0.009

r = Correlation coefficient

Abbreviations: UN/Cre ratio, urea nitrogen-to-creatinine ratio; HR, hazard ratio; CI, confidence interval.

Table 4 Results of multivariate linear regression analyses of the log-transformed UN/Cre ratio

	Model 1			Model 2		
Variables	**β coefficient**	**95% CI**	**P value**	**β coefficient**	**95% CI**	**P value**
Age (year)	0.008	0.005–0.010	<0.001	0.008	0.005–0.010	<0.001
Gender (female vs. male)	0.16	0.11–0.21	<0.001	0.16	0.11–0.21	<0.001
Dialysis vintage (years)	−0.002	−0.004–0.001	0.13	−0.002	−0.005–0.001	0.15
Diabetes mellitus (%)	0.06	0.01–0.11	0.01	0.08	0.03–0.14	0.001
CVD history (%)	0.003	−0.04–0.05	0.9	0.01	−0.04–0.06	0.6
Smoking (%)	−0.006	−0.06–0.05	0.82	−0.03	−0.08–0.03	0.6
Clinical frailty scale						
Mild frail vs. non-frail	0.01	−0.04–0.07	0.62	0.02	−0.04–0.07	0.53
Severe frail vs. non-frail	0.07	−0.003–0.147	0.06	0.05	−0.03–0.13	0.24
Renal rehabilitation at baseline	0.005	−0.04–0.05	0.82	−0.001	−0.05–0.05	0.95

RAS inhibitor use (%)	—	−0.03	−0.08–0.01	0.14
Statin use (%)	—	−0.04	−0.09–0.01	0.08
Systolic blood pressure (mmHg)	—	−0.001	$-0.002–5.2\times10^{-6}$	0.05
Albumin (g/dL)	—	0.04	−0.04–0.11	0.35
Hemoglobin (g/dL)	—	−0.03	−0.05 to −0.01	0.01
Log-transformed C-reactive protein (mg/L)	—	0.007	−0.01–0.03	0.46

Abbreviations: UN/Cre ratio, urea nitrogen-to-creatinine ratio; CI, confidence interval; CVD, cardiovascular disease; RAS, renin-angiotensin system.

Discussion

Although we hypothesized that exercise intervention would decrease the UN/Cre ratio by reducing catabolic stress and improving PEW, our findings did not demonstrate a significant association between renal rehabilitation and longitudinal changes in the UN/Cre ratio. In contrast, a higher UN/Cre ratio was significantly associated with all-cause mortality after adjustment for several clinical parameters, including renal rehabilitation status. Furthermore, a higher UN/Cre ratio was associated with several clinical characteristics, including female sex, diabetes mellitus, nonsmoking status, greater frailty, older age, lower systolic blood pressure, lower serum albumin and hemoglobin levels, and higher log-transformed CRP levels. In multivariable linear regression analyses, older age, female sex, diabetes mellitus, and lower hemoglobin levels were independently associated with a higher UN/Cre ratio.

Theoretically, exercise therapy may decrease the UN/Cre ratio through several potential mechanisms. First, exercise therapy may increase or preserve skeletal muscle mass, which is a major determinant of creatinine generation. In particular, in anuric patients undergoing HD, in whom serum creatinine is largely unaffected by renal clearance, lean body mass has been reported to correlate strongly with pre-dialysis serum creatinine levels.[9,10] Consistent with this concept, the creatinine index proposed by Canaud et al. has been developed and widely used as an indirect marker of muscle mass in patients undergoing HD; this index incorporates serum creatinine together with age, sex, and Kt/Vurea.[11] Thus, preservation or improvement of skeletal muscle mass through exercise therapy could potentially increase creatinine generation and consequently contribute to a reduction in the UN/Cre ratio.

Second, intradialytic exercise may enhance urea removal and improve markers of dialysis adequacy, such as Kt/Vurea and the urea reduction ratio (URR). Several studies, including meta-analyses, have suggested that intradialytic exercise may improve Kt/Vurea and URR.[12,13] One proposed mechanism is that exercise increases skeletal muscle blood flow, thereby promoting the mobilization of urea sequestered in the interstitial compartment back into the intravascular space and facilitating its removal across the dialysis membrane. In addition, exercise-induced increases in cardiac output and circulating blood volume may increase solute delivery to the dialyzer and thereby enhance diffusive clearance. Nevertheless, the extent to which the effect on solute clearance differs according to exercise modality remains uncertain. Although aerobic exercise, resistance training, and combined exercise have all been investigated, the combination of aerobic and resistance exercise may be particularly effective based on theoretical considerations and findings from a network meta-analysis.[14]

Third, exercise therapy may attenuate protein catabolism and urea generation by reducing inflammation and improving metabolic status, which could also contribute to a reduction in the UN/Cre ratio.[7,13,15] In the present study, higher UN/Cre ratios were associated with several markers consistent with an inflammatory and catabolic state, including older age, lower serum albumin and hemoglobin levels, higher CRP levels, and greater frailty. These findings are broadly consistent with the hypothesis that the UN/Cre ratio may reflect not only protein intake but also the systemic catabolic state and the complex nutritional and inflammatory milieu characteristic of malnutrition-inflammation-atherosclerosis (MIA) syndrome in patients undergoing HD.[16] Among the factors examined, hemoglobin was the only potentially modifiable factor that remained

independently and inversely associated with the UN/Cre ratio. Although the underlying mechanisms remain uncertain, these findings suggest that the UN/Cre ratio may capture multiple aspects of nutritional, inflammatory, and muscle-related status rather than reflecting a single physiological process.

Despite the rationale described above, we did not observe a significant longitudinal reduction in the UN/Cre ratio associated with exercise therapy. This finding was contrary to our expectation and to the results of a previous randomized controlled trial, which demonstrated a reduction in the UN/Cre ratio following intradialytic exercise therapy.[7] These findings suggest that the UN/Cre ratio may not be a sufficiently sensitive marker for detecting the effects of exercise therapy on nutritional or catabolic status in patients undergoing maintenance HD. Rather, our findings suggest that multiple physiological processes, including muscle mass, urea generation, solute clearance, inflammation, and nutritional status, may contribute to changes in the UN/Cre ratio, and that these factors may operate independently of the effects of exercise therapy. Nevertheless, our findings do not exclude a potential association between exercise therapy and the UN/Cre ratio. First, we did not separately evaluate the effects of different exercise modalities, including aerobic exercise, resistance training, or combined exercise, on longitudinal changes in the UN/Cre ratio. Second, adherence to exercise therapy, as well as the intensity and duration of exercise, was not incorporated into the analysis. These factors may influence the physiological effects of exercise and could potentially modify its effect on the UN/Cre ratio. Therefore, future prospective studies with standardized exercise protocols and detailed assessment of exercise modality, intensity,

duration, and adherence are warranted to clarify whether and under what conditions exercise therapy influences the UN/Cre ratio.

Nonetheless, consistent with previous studies, a higher UN/Cre ratio was significantly and independently associated with higher mortality among patients undergoing HD. In the Q-Cohort study, which included 3,401 patients undergoing maintenance HD who were followed for 4 years, a higher UN/Cre ratio was associated with increased all-cause mortality, as well as a higher risk of coronary heart disease.[5] Similarly, in another Japanese multicenter cohort of 1,321 patients undergoing HD, patients in the highest UN/Cre ratio group (>6.8) had significantly higher mortality than those in the reference group (UN/Cre ratio, 4.7–5.6).[6] Our findings further support the prognostic significance of the UN/Cre ratio for mortality in patients undergoing HD. Our study also has several notable features. First, we included intradialytic renal rehabilitation and clinical frailty as potential confounders in the multivariable analyses, based on the approach used in the main REVEAL-D study.[8] In particular, greater clinical frailty was associated with a higher UN/Cre ratio in the univariable analysis. Nevertheless, the association between a higher UN/Cre ratio and mortality remained significant after adjustment for clinical frailty and other relevant clinical factors. These findings suggest that the prognostic significance of the UN/Cre ratio is not fully explained by differences in clinical frailty and may provide prognostic information beyond frailty status in patients undergoing HD.

There are several limitations to this study. First, this was a retrospective observational study, and several sources of bias, including selection bias, cannot be excluded. Although the multivariable analyses included several clinical parameters

associated with mortality, the possibility of residual confounding remains. Second, although approximately 700 patients from multiple regions across Japan were included, the study population may not fully represent the broader population of Japanese patients undergoing HD. Furthermore, to our knowledge, together with previous studies,[5,6] the association between the UN/Cre ratio and mortality has been demonstrated only in Japanese populations. Therefore, the clinical significance and generalizability of the UN/Cre ratio in other countries and ethnic populations remain uncertain. Third, because of the retrospective study design, several clinically important parameters could not be adequately evaluated because of substantial missing data. These included Kt/Vurea, which could have provided additional information regarding protein catabolism. Similarly, measures of physical function and exercise capacity, including handgrip strength, the Short Physical Performance Battery, and the Five Times Sit-to-Stand Test, were not available for a substantial proportion of patients. Prospective studies or prospective registries with standardized and systematic collection of these parameters and minimal missing data are warranted. Fourth, although we evaluated the association between intradialytic renal rehabilitation and the UN/Cre ratio, the renal rehabilitation program in REVEAL-D comprised not only intradialytic exercise but also nutritional counseling, lifestyle guidance, and patient engagement. Therefore, we could not separately assess the effects of these non-exercise components on the UN/Cre ratio or determine whether the observed associations were attributable primarily to exercise or to other components of the rehabilitation program. Future prospective studies with more clearly defined rehabilitation components are warranted to clarify the respective contributions of these interventions. Finally, because of the observational nature of this study, our findings do not establish a causal relationship between the UN/Cre ratio and

mortality in patients undergoing HD. Although the UN/Cre ratio was significantly associated with mortality, it remains unclear whether modifying the UN/Cre ratio itself can improve clinical outcomes. Furthermore, despite our hypothesis that intradialytic renal rehabilitation might modify the UN/Cre ratio, we did not demonstrate a significant longitudinal association in the present study. Thus, the clinical utility of the UN/Cre ratio as a modifiable treatment target remains uncertain. Future studies should further clarify the clinical factors associated with longitudinal changes in the UN/Cre ratio and determine whether interventions targeting these factors can modify the UN/Cre ratio and, ultimately, improve clinical outcomes.

In conclusion, in this Japanese retrospective cohort of 695 patients undergoing HD, we did not demonstrate a clear association between intradialytic renal rehabilitation and longitudinal changes in the UN/Cre ratio. Although the UN/Cre ratio may reflect the complex nutritional and inflammatory milieu characteristic of MIA syndrome and was independently associated with all-cause mortality, its clinical significance as a modifiable marker for improving clinical outcomes remains uncertain. Future well-designed prospective studies or registries with standardized data collection and minimal missing data are warranted to further elucidate the clinical significance and modifiability of the UN/Cre ratio.

List of abbreviations

ANOVA, analysis of variance; BMI, body mass index; CFS, Clinical Frailty Scale; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; DM,

diabetes mellitus; HD, hemodialysis; HDF, hemodiafiltration; HR, hazard ratio; MIA, malnutrition-inflammation-atherosclerosis; PEW, protein-energy wasting; PTH, parathyroid hormone; RAS, renin–angiotensin system; REVEAL-D, Registry of Active Renal Rehabilitation in Dialysis Patients; SEM, standard error of the mean; UN/Cre ratio, urea nitrogen-to-creatinine ratio; URR, urea reduction ratio.

Data Availability

Due to ethical restrictions and patient confidentiality, the data used in this study are not publicly available. However, de-identified data may be available upon reasonable request to the corresponding author.

Declaration of Conflicting Interest

The authors declare no conflicts of interest. Dr. Junichi Hoshino is an Associate Editor, and Dr. Ichiei Narita is a member of the Editorial Board of this journal.

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Ethical Approval

The protocol for this study was reviewed and approved by the Ethics Committee of Tokyo Women's Medical University (approval number: 2023-0204).

Informed Consent to Participate

The requirement for informed consent was waived because of the retrospective study design and the use of deidentified patient data.

Informed Consent for Publication

Not applicable.

Clinical Trial Number

Not applicable.

CRediT Author Statement

Kiyotaka Uchiyama: Conceptualization, Formal analysis, Writing – original draft. Go Owari: Formal analysis, Writing – original draft. Kenta Kanda: Formal analysis. Kenichi Kono: Investigation. Keisuke Kida: Investigation. Tadashi Sofue: Investigation.

Junichi Hoshino: Investigation. Kunihiro Yamagata: Writing – review & editing. Ichiei Narita: Writing – review & editing, Supervision.

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Disclosure

We, on behalf of all authors, confirm that GPT-5 was used to assist with research and manuscript preparation. These tools were used for assistance in Language & Writing (Improving grammar and language, Paraphrasing and rewording, Adjusting tone and

style, Formatting citations and references). We confirm that we had full oversight of all assisted work and confirm the validity of the related sections in the submission. We confirm that AI tools are not listed as authors. Submitted by: Kiyotaka Uchiyama

References

1. Gui S, Zou Z, He X. Association between blood urea nitrogen-to-creatinine ratio and 28-day mortality in acute kidney injury patients undergoing continuous renal replacement therapy. Sci Rep. 2025;16(1):1478.
2. Cabanillas-Lazo M, Sernaqué-Mechato RA, Montes-Baldarrago A, et al. Clinical value of blood urea to creatinine ratio in heart failure patients: a systematic review. Clin Cardiol. 2026;49(5):e70344.
3. Aronson D, Hammerman H, Beyar R, et al. Serum blood urea nitrogen and long-term mortality in acute ST-elevation myocardial infarction. Int J Cardiol. 2008;127(3):380–5.
4. Luwen H, Qin C, Lei X, Ming Y, Linlin L. Elevated blood urea nitrogen-to-creatinine ratio predicts short-term mortality in intensive care unit patients with ischemic stroke: evidence from a multicenter cohort. PLoS One. 2025;20(12):e0337807.
5. Tanaka S, Ninomiya T, Taniguchi M, et al. Impact of blood urea nitrogen to creatinine ratio on mortality and morbidity in hemodialysis patients: the Q-Cohort Study. Sci Rep. 2017;7(1):14901.
6. Tanimoto S, Nakashima A, Kato K, et al. Impact of blood urea nitrogen to creatinine ratio on infectious events, cardiovascular events, and all-cause mortality in patients with hemodialysis: a retrospective cohort study. Ren Replace Ther. 2025;11:60.

7. Nakoui N, Ilbeigi S, Ahmadi MM, Saber A. Comparison of the effect of aerobic and resistance training on fatigue, quality of life and biochemical factors in hemodialysis patients. Sci Rep. 2025;15:10052.
8. Hoshino J, Kida K, Kobayashi S, et al. Intradialytic renal rehabilitation and mortality: results from the registry of active renal rehabilitation in dialysis patients (REVEAL-D). Clin J Am Soc Nephrol. 2026. doi: 10.2215/CJN.0000001133.
9. Patel SS, Molnar MZ, Tayek JA, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. J Cachexia Sarcopenia Muscle. 2013;4(1):19–29.
10. Vodičar J, Pajek J, Hadžić V, Bučar Pajek M. Relation of lean body mass and muscle performance to serum creatinine concentration in hemodialysis patients. Biomed Res Int. 2018;2018:4816536.
11. Canaud B, Granger Vallée A, et al. Creatinine index as a surrogate of lean body mass derived from urea Kt/V, pre-dialysis serum levels and anthropometric characteristics of haemodialysis patients. PLoS One. 2014;9(3):e93286.
12. Ferreira GD, Bohlke M, Correa CM, Dias EC, Orcy RB. Does intradialytic exercise improve removal of solutes by hemodialysis? A systematic review and meta-analysis. Arch Phys Med Rehabil. 2019;100(12):2371–80.
13. Boukadida R, Saadaoui M, Thabet N, et al. The effect of intradialytic resistance exercise on physical function and dialysis adequacy in patients on maintenance hemodialysis. PLoS One. 2026;21(3):e0337910.
14. Hu H, Wu C, Kwok JYY, et al. Effects of different exercises on physical function, dialysis adequacy, and health-related quality of life in maintenance hemodialysis

patients: a systematic review and network meta-analysis. Am J Nephrol. 2023;54(9–10):379–90.

15. Rahbar Saadat Y, Abbasi A, Hejazian SS, et al. Combating chronic kidney disease-associated cachexia: a literature review of recent therapeutic approaches. BMC Nephrol. 2025;26(1):133.
16. Noor H, Ganesan S, Cantarutti FM, et al. Prevalence and overlap of malnutrition, sarcopenia and related nutritional syndromes in a large haemodialysis population. J Cachexia Sarcopenia Muscle. 2026;17(5):e70386.

Figure Legends

Figure 1. Flowchart of patient selection for this study.

Abbreviations: REVEAL-D, Registry of Active Renal Rehabilitation in Dialysis; UN, urea nitrogen.

Figure 2. Longitudinal changes in the UN/Cre ratio according to renal rehabilitation status, estimated using linear mixed-effects models. (A) Analysis based on baseline renal rehabilitation status. (B) Analysis based on longitudinal renal rehabilitation status.

Abbreviations: UN/Cre ratio, urea nitrogen-to-creatinine ratio.

Data are presented as mean ± standard error of the mean (SEM).

Figures

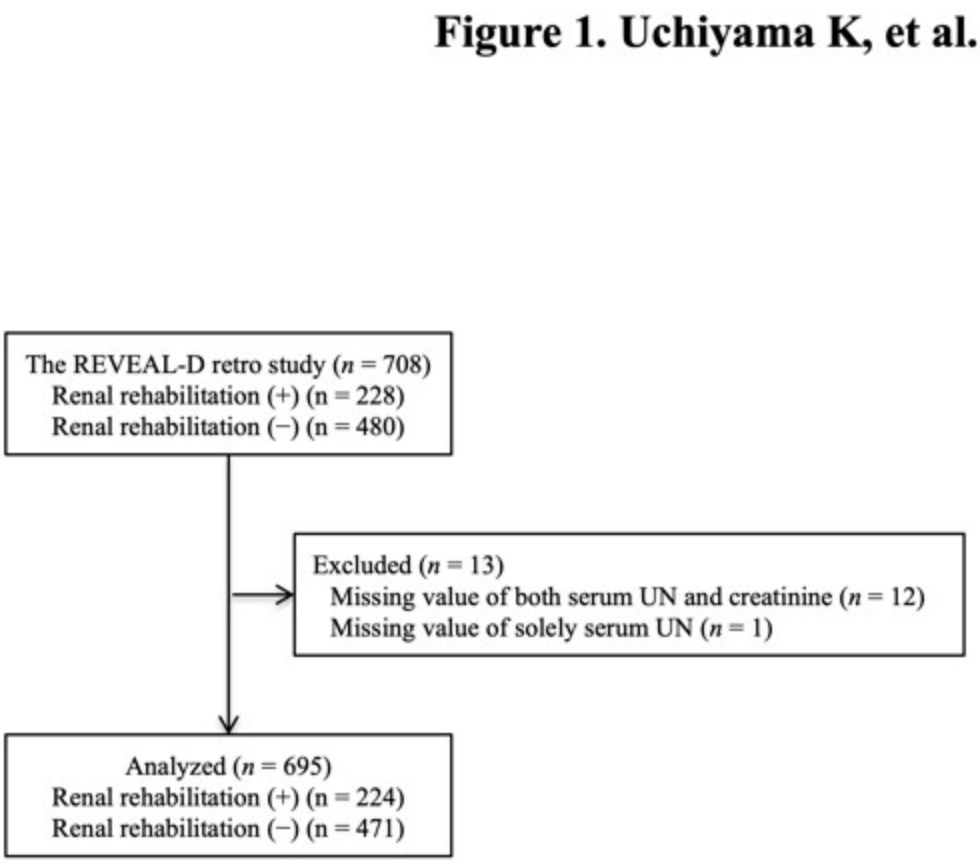


Figure 1

Flowchart of patient selection for this study.

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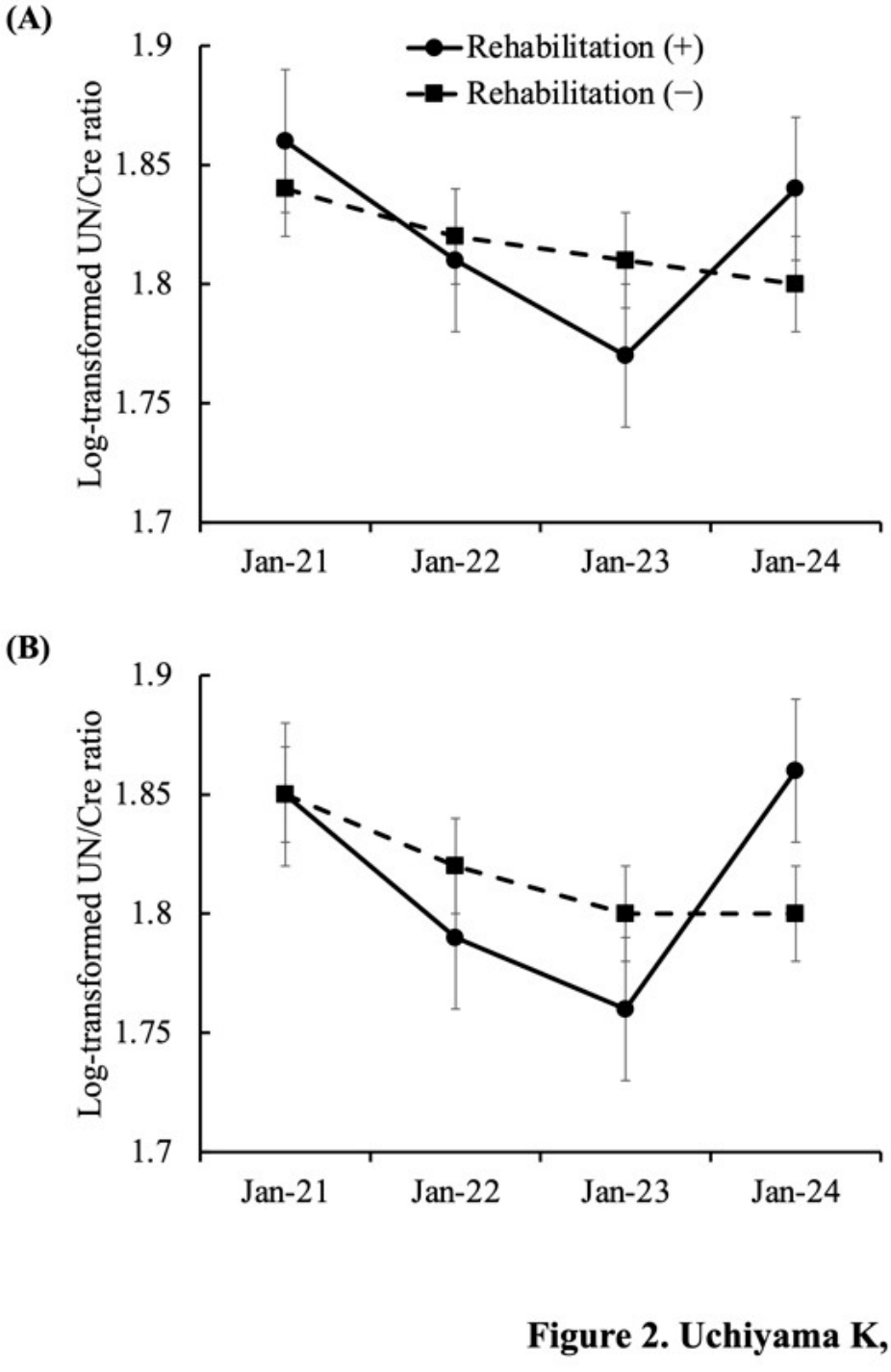


Figure 2. Uchiyama K, et al.

Figure 2

Longitudinal changes in the UN/Cre ratio according to renal rehabilitation status, estimated using linear mixed-effects models. (A) Analysis based on baseline renal rehabilitation status. (B) Analysis based on longitudinal renal rehabilitation status.

Abbreviations: UN/Cre ratio, urea nitrogen-to-creatinine ratio.

Data are presented as mean ± standard error of the mean (SEM).