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Modified creatinine index and risk for cardiovascular events and all-cause mortality in patients undergoing hemodialysis: The Q-Cohort study

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ABSTRACT

Background and aims: The modified creatinine (Cr) index, calculated by age, sex, pre-dialysis serum Cr levels, and Kt/V for urea, reflects skeletal muscle mass in patients on hemodialysis. Whether the modified Cr index is associated with cardiovascular events and all-cause mortality remains unknown.
Methods: A total of 3027 patients registered in the Q-Cohort Study, a multicenter, prospective study of patients on hemodialysis in Japan, were analyzed. The main outcomes were cardiovascular events and all-cause mortality. Associations between sex-specific quartiles of the modified Cr index and outcomes were analyzed by the Cox proportional hazard models and the Fine–Gray proportional subdistribution hazards model.
Results: The modified Cr index was correlated with known nutritional and inflammatory markers. During a 4-year follow-up, 499 patients died of any cause, 372 experienced heart disease, and 194 developed stroke. The risk for all-cause mortality was significantly higher in the lower quartiles (Q1 and Q2) than in the highest quartile (Q4) as the reference group (hazard ratios and 95% confidence intervals: Q1, 2.65 [1.69–4.25], Q2, 1.92 [1.27–2.94], and Q3, 1.31 [0.87–2.02]). The risk of heart disease was significantly higher in Q1 than in Q4 (hazard ratios and 95% confidence intervals: Q1, 1.64 [1.04–2.61], Q2, 1.34 [0.91–2.00], and Q3, 1.04 [0.71–1.52]). The risk of stroke was not associated with the modified Cr index.
Conclusions: A lower modified Cr index is associated with an increased risk for heart disease and all-cause mortality, but not with the risk for stroke in patients on hemodialysis.

1. Introduction

Patients on hemodialysis (HD) are at increased risk of death compared with the general population, and cardiovascular events are the leading cause of mortality in patients on HD worldwide [1,2]. Although great effort has been made to control risk factors for cardiovascular events and mortality, such as hemoglobin [3,4], blood pressure [5] and diabetes mellitus [6,7], the mortality rate of the HD population is still unacceptably high. Therefore, determining modifiable risk factors for cardiovascular events and mortality in patients receiving HD is important.

Malnutrition is a fundamental risk factor for morbidity and mortality [8,9]. Several lines of evidence have shown that malnutrition is highly prevalent among the HD population compared with the general population [10,11]. Additionally, malnutrition augments

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the risk for cardiovascular events [12]. Such a negative effect of malnutrition on morbidity and mortality in the HD population has recently been conceptualized as malnutrition–inflammation–atherosclerosis (MIA) syndrome or malnutrition–inflammation complex syndrome (MICS) [13,14]. MIA and MICS greatly increase the risk for cardiovascular events and all-cause mortality. Therefore, identifying simple and accurate surrogate makers for MIA and MICS in patients on HD is clinically relevant.

Several studies have shown that a decrease in skeletal muscle mass is associated with worse prognosis in patients on HD [15]. The creatinine (Cr) index, which is derived from Cr kinetic modeling, is a convenient indicator of skeletal muscle mass, and is subject to periodical screening of skeletal muscle mass [16]. Notably, previous studies showed an association between the original Cr index and all-cause mortality in patients on HD [17,18]. Recently, the modified Cr index, a simpler version of the original Cr index, was introduced as another surrogate of skeletal muscle mass [19,20]. The modified Cr index is determined by age, sex, pre-dialysis serum Cr levels, and Kt/V for urea, and has recently been shown to predict all-cause mortality of patients on HD. Malnutrition induces hypercatabolism of skeletal muscle and often involves decreased skeletal muscle mass and function, known as sarcopenia [21]. Therefore, we hypothesized that the modified Cr index reflects MIA and MICS, and thus can predict a patient's diverse outcomes other than mortality. However, the association between the modified Cr index and several types of cardiovascular events in the HD population is still unclear.

The present study aimed to examine the relationships between skeletal muscle mass and cardiovascular events and all-cause mortality in patients on HD. We determined the associations between the modified Cr index and the risks for cardiovascular events and all-cause mortality in patients on HD by analyzing data derived from the Q-Cohort Study.

2. Materials and methods

2.1. Design of the Q-Cohort study

The Q-Cohort Study was a multicenter, prospective, longitudinal, observational study that was designed to identify risk factors for morbidity and mortality in patients with end-stage renal disease undergoing prevalent HD in Japan [22–25]. Briefly, the study population consisted of 3598 outpatients who were ≥18 years old and underwent regular HD therapy between December 2006 and December 2007 at 39 dialysis facilities. All of the patients were scheduled to be followed up until December 2010. Patients who were lost to follow-up during the observation period were regarded as “censored” on the day of the final visit, and were also included in the analyses. Of the 3598 patients, 571 were excluded because of missing data of either baseline characteristics or outcomes. Therefore, data from 3027 patients were analyzed in the study. The study was performed according to the Ethics of Clinical Research (1975 Declaration of Helsinki). The study protocol was approved by the Kyushu University Hospital Institutional Review Board for Clinical Research (No. 20–31), and was registered in a clinical trial registry (University Hospital Medical Information Network, UMIN000000556). All of the patients provided written informed consent prior to participation in the study.

2.2. Demographic factors and biochemical measurements

Demographic and clinical data at baseline were recorded at enrollment. These data included age, sex, presence of diabetic nephropathy, history of cardiovascular events and bone fractures, dialysis vintage, dialysis time, body mass index, normalized protein catabolic rate (nPCR), systolic blood pressure, cardiothoracic ratio, and use of erythropoiesis-stimulating agents, anti-hypertensives, phosphate-binders, and vitamin D receptor activators. Blood samples were collected just before starting dialysis sessions after a 2-day inter-dialytic interval from vascular access. Hematological and biochemical parameters were measured using the collected blood at the time of enrolment. Routine hematological and biochemical parameters, including hemoglobin, serum levels of albumin, total cholesterol, C-reactive protein (CRP), urea nitrogen, Cr, calcium, phosphate, and alkaline phosphatase, were measured using an auto-analyzer with standard procedures at different laboratories depending on the location of the dialysis centers. Serum parathyroid hormone (PTH) levels were measured using whole or intact PTH assays. Conversion between the two assays was conducted using the following equation: intact PTH (pg/mL) = 1.7 × whole PTH (pg/mL) [26]. Corrected serum calcium levels were calculated depending on serum albumin levels based on Payne's formula: corrected serum calcium = serum calcium level + (4 − serum albumin level) [27]. Single-pool Kt/V for urea was used as the indicator of adequacy of dialysis. In the present study, residual renal function (RRF) was not measured and not considered when Kt/V for urea was calculated.

2.3. Definition of outcomes and covariates

Heart disease, stroke, and all-cause death were the main outcomes in this study. Heart disease included first-ever development of myocardial infarction, hospitalization for unstable angina, coronary intervention (coronary artery bypass surgery or angioplasty), and hospitalization for heart failure. Stroke was composed of ischemic stroke (brain infarction) and hemorrhagic stroke (brain hemorrhage). Definitions of each disease were described in detail previously [23,24]. The covariate of interest was the modified Cr index [19,20], which is a simple, precise, and cost-effective tool used to estimate skeletal muscle mass in patients undergoing HD. In the present study, the modified Cr index was calculated by the following formula based on age, sex, pre-dialysis serum Cr concentrations, and Kt/V for urea: modified Cr index (mg/kg/day) = 16.21 + 1.12 × [1 if male; 0 if female] − 0.06 × age (years) − 0.08 × single-pooled Kt/V for urea + 0.009 × serum Cr level before dialysis (μmol/L) [19,20]. The difference between the original modified Cr index and our modified Cr index is that our modified Cr index used pre-dialysis serum Cr levels that were measured on the first dialysis day of the week. However, the original modified Cr index used pre-dialysis serum Cr levels that were measured on the second dialysis day of the week. We confirmed a good correlation of the modified Cr index calculated by the previous formula with skeletal muscle mass as measured by bioelectrical impedance analysis in an independent cohort [20].

2.4. Statistical analysis

Normally and non-normally distributed continuous variables are described as median and interquartile range, and categorical data are described as number and percentage. Because distribution of the modified Cr index varied according to sex, subjects were categorized into quartiles (Q1–Q4) based on a sex-specific modified Cr index. The distribution of baseline characteristics divided by quartiles of the modified Cr index was compared using trend analyses; the Cochran–Armitage test was used for categorical variables and the Jonckheere–Terpstra test for continuous variables. Simple correlations between the modified Cr index and serum albumin levels, body mass index, and nPCR were analyzed by using Pearson's correlation coefficient. Simple correlations between the

modified Cr index and serum CRP levels were analyzed by using Spearman's rank correlation coefficient. The event-free survival rates for cardiovascular events and all-cause mortality according to sex-specific modified Cr index quartiles were examined using the Kaplan–Meier method and compared by the log-rank test. Unadjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes were estimated using the Cox proportional hazards model. The Fine–Gray proportional subdistribution hazards model with all-cause death as a competing risk was also used to assess outcome. The assumption of proportional hazards was checked graphically using log cumulative hazard plots for each outcome according to the modified Cr index. Multivariable-adjusted models included the following covariates: age, sex, presence of diabetic nephropathy, history of cardiovascular events and bone fractures, dialysis vintage, dialysis time, systolic blood pressure, cardiothoracic ratio, nPCR, Kt/V for urea, body mass index, hemoglobin, serum levels of albumin, total cholesterol, urea nitrogen, CRP, corrected calcium, phosphate, alkaline phosphatase, and PTH, and use of erythropoiesis-stimulating agents, anti-hypertensives, phosphate-binders, and vitamin D receptor activators. Variables in the multivariable-adjusted models were based on *a priori* clinical judgment. We also analyzed the non-linear relationships between the modified Cr index and outcomes by setting the modified Cr index as a continuous variable and fitting a restricted cubic spline model. A two-tailed p value < 0.05 was considered statistically significant in all analyses. Statistical analyses were performed using JMP version 13.2 (SAS Institute, Cary, NC, USA) and R software version 3.0.2 (http://cran.rproject.org).

Table 1
Clinical backgrounds at baseline and outcomes during the observation period in each group stratified according to sex-specific modified creatinine index quartiles ($n = 3027$).

	Sex-specific quartiles of modified Cr index, mg/kg/day				
	Q1	Q2	Q3	Q4	p for trend
	M: −20.34	M: 20.35–22.13	M: 22.14–24.02	M: 24.03–	
	F: −17.95	F: 17.96–19.43	F: 19.44–20.96	F: 20.97–	
Baseline characteristics	n = 755	n = 758	n = 757	n = 757	
Demographics and dialysis-related information					
Modified Cr index, mg/kg/day	17.9 (16.9–19.4)	20.7 (18.9–21.4)	22.4 (20.4–23.1)	24.4 (22.4–25.6)	<0.001
Age, years	75.0 (68.8–80.7)	68.7 (61.9–74.5)	62.3 (56.8–67.3)	52.9 (44.3–58.9)	<0.001
Female sex	308 (40.8)	309 (40.8)	307 (40.6)	310 (41.0)	0.97
Diabetic nephropathy	307 (40.7)	266 (35.1)	194 (25.6)	103 (13.6)	<0.001
History of cardiovascular events	248 (32.9)	200 (26.4)	151 (20.0)	97 (12.8)	<0.001
History of bone fractures	132 (17.5)	73 (9.6)	57 (7.5)	39 (5.2)	<0.001
Dialysis vintage, year	2.8 (0.8–6.8)	4.7 (1.9–10.9)	7.2 (3.1–12.8)	8.3 (4.2–14.5)	<0.001
Dialysis time (≧5 h)	391 (51.8)	470 (62.0)	512 (67.6)	503 (66.5)	<0.001
Kt/V for urea	1.6 (1.4–1.7)	1.6 (1.4–1.8)	1.6 (1.4–1.7)	1.6 (1.4–1.7)	0.65
Body mass index, kg/m^2	19.7 (18.0–22.0)	20.9 (18.9–23.0)	21.0 (19.1–23.0)	21.6 (19.6–23.8)	<0.001
nPCR, g/kg/day	0.9 (0.8–1.0)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	<0.001
Systolic blood pressure, mmHg	152 (138–169)	155 (140–170)	154 (140–168)	151 (136–165)	0.02
Cardiothoracic ratio, %	52.2 (48.0–56.5)	50.7 (47.3–54.2)	50.0 (46.9–53.1)	48.8 (45.9–51.8)	<0.001
Blood tests					
Hemoglobin, g/dL	10.3 (9.6–11.1)	10.6 (9.7–11.2)	10.6 (9.9–11.3)	10.7 (10.0–11.4)	<0.001
Serum albumin, g/dL	3.6 (3.3–3.9)	3.8 (3.5–4.0)	3.9 (3.7–4.1)	4.0 (3.8–4.2)	<0.001
Serum total cholesterol, mg/dL	150 (128–176)	152 (131–179)	152 (130–180)	152 (130–177)	0.59
Serum urea nitrogen, mg/dL	57 (47–68)	64 (56–73.3)	69 (60–78)	73 (65–82)	<0.001
Serum Cr, mg/dL	7.3 (6.4–8.2)	9.5 (8.7–10.4)	11.2 (10.1–12.1)	13.3 (11.9–14.5)	<0.001
Serum C-reactive protein, mg/dL	0.2 (0.1–0.6)	0.1 (0.1–0.4)	0.1 (0.1–0.3)	0.1 (0–0.2)	<0.001
Corrected serum Ca, mg/dL	9.2 (8.8–9.7)	9.3 (8.9–9.8)	9.5 (8.9–10.0)	9.5 (9.0–10.0)	<0.001
Serum phosphate, mg/dL	4.4 (3.7–5.1)	4.8 (4.1–5.5)	5.1 (4.4–5.8)	5.3 (4.6–6.1)	<0.001
Serum alkaline phosphatase, U/L	257 (204–344)	242 (189–315)	225 (177–304)	209 (161–281)	<0.001
Serum PTH (intact assay), pg/mL	86 (40–156)	103 (44–207)	104 (46–215)	129 (57–254)	<0.001
Medications					
Use of phosphate binders	476 (63.1)	625 (82.5)	672 (88.8)	703 (92.3)	<0.001
Use of VDRAs	474 (62.8)	537 (70.9)	567 (74.9)	567 (74.9)	<0.001
Use of anti-hypertensives	484 (64.1)	501 (66.1)	484 (63.9)	464 (61.3)	0.18
Use of ESAs	679 (89.9)	648 (85.5)	629 (83.1)	591 (78.1)	<0.001
Outcomes during the observation period	n = 755	n = 758	n = 757	n = 757	
All-cause death	253 (33.5)	138 (18.2)	73 (9.6)	35 (4.6)	<0.001
Heart disease	132 (17.5)	112 (14.8)	76 (10.0)	52 (6.9)	<0.001
Brain infarction	38 (5.0)	48 (6.3)	27 (3.6)	15 (2.0)	<0.001
Brain hemorrhage	12 (1.6)	12 (1.6)	23 (3.0)	19 (2.5)	0.08

Baseline data are expressed as the median (interquartile range) or number (percentage). Outcomes during the observation period are expressed as number (percentage). The Cochran–Armitage test was used to determine p for trend of categorical variables. The Jonckheere–Terpstra test was used to determine p for trend of continuous variables. A two-tailed p-value <0.05 was considered statistically significant.
Cr, creatinine; ESAs, erythropoiesis stimulating agents; Ca, calcium; F, female; M, male; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; Q, quartile of the modified Cr index; VDRAs, vitamin D receptor activators. Conversion factors for units: hemoglobin in g/dL to g/L, ×10; albumin in g/dL to g/L, ×10; total cholesterol in mg/dL to mmol/L, ×0.0259; urea nitrogen in mg/dL to mmol/L, ×0.357; creatinine in mg/dL to μmol/L, ×88.4; C-reactive protein in mg/dL to nmol/L, ×9.524; albumin-corrected Ca in mg/dL to mmol/L, ×0.25; phosphate in mg/dL to mmol/L, ×0.323; PTH in pg/mL to ng/L, ×1.

3. Results

3.1. Baseline characteristics according to sex-specific modified Cr index quartiles

All data were stratified according to sex-specific quartiles of the modified Cr index (Table 1). Patients with a lower modified Cr index had a significantly older age, higher prevalence of diabetic nephropathy and a history of cardiovascular events and bone fractures, shorter dialysis vintage and dialysis time, lower body mass index and nPCR, and higher cardiothoracic ratio. Serum levels of CRP and alkaline phosphatase were significantly higher in patients with a lower modified Cr index. However, hemoglobin and serum levels of albumin, urea nitrogen, Cr, corrected calcium, phosphate, and PTH were significantly lower in patients with a lower modified Cr index. Patients with a lower modified Cr index used phosphate binders and vitamin D receptor activators significantly less frequently, whereas they used erythropoiesis-stimulating agents significantly more frequently.

Simple correlation coefficients were determined to examine the association between the modified Cr index and serum MICS markers. The modified Cr index was significantly positively correlated with serum albumin levels, body mass index, and nPCR, whereas it was significantly negatively correlated with serum CRP levels (Fig. 1).

3.2. Association between the modified Cr index and the risks for cardiovascular events and all-cause mortality

During a median 4 years (interquartile range: 1035–1440 days) of observational period, 372 patients newly developed heart disease, 194 newly developed stroke, including brain infarction of 128 patients and brain hemorrhage of 66 patients, and 499 died of any cause. The incidence of heart disease, brain infarction, and all-cause death was highest in the lowest modified Cr index quartiles (Q1), whereas the incidence of brain hemorrhage was not significantly different among the quartiles (Table 1). Kaplan–Meier curves showed significantly higher incidence rates of heart disease, brain infarction, and all-cause death at lower modified Cr index quartiles than at higher modified Cr index quartiles (heart disease, $p < 0.01$; brain infarction, $p < 0.01$; all-cause death, $p < 0.01$; log-rank test, Fig. 2). However, the incidence rate of brain hemorrhage was not significantly different across the four quartiles stratified by the modified Cr index (brain hemorrhage, $p = 0.40$; log-rank test, Fig. 2).

In the unadjusted and multivariable-adjusted Cox proportional hazards models, patients with lower modified Cr index quartiles (Q1 and Q2) showed higher adjusted HRs for the incidence rate of all-cause death compared with the reference group (Q4) (Table 2). The HR (95% CI) for a 1 mg/kg/day decrease in the modified Cr index was 1.19 (1.11–1.27, $p < 0.01$). In the unadjusted and multivariable-adjusted Cox proportional hazards models, patients with the

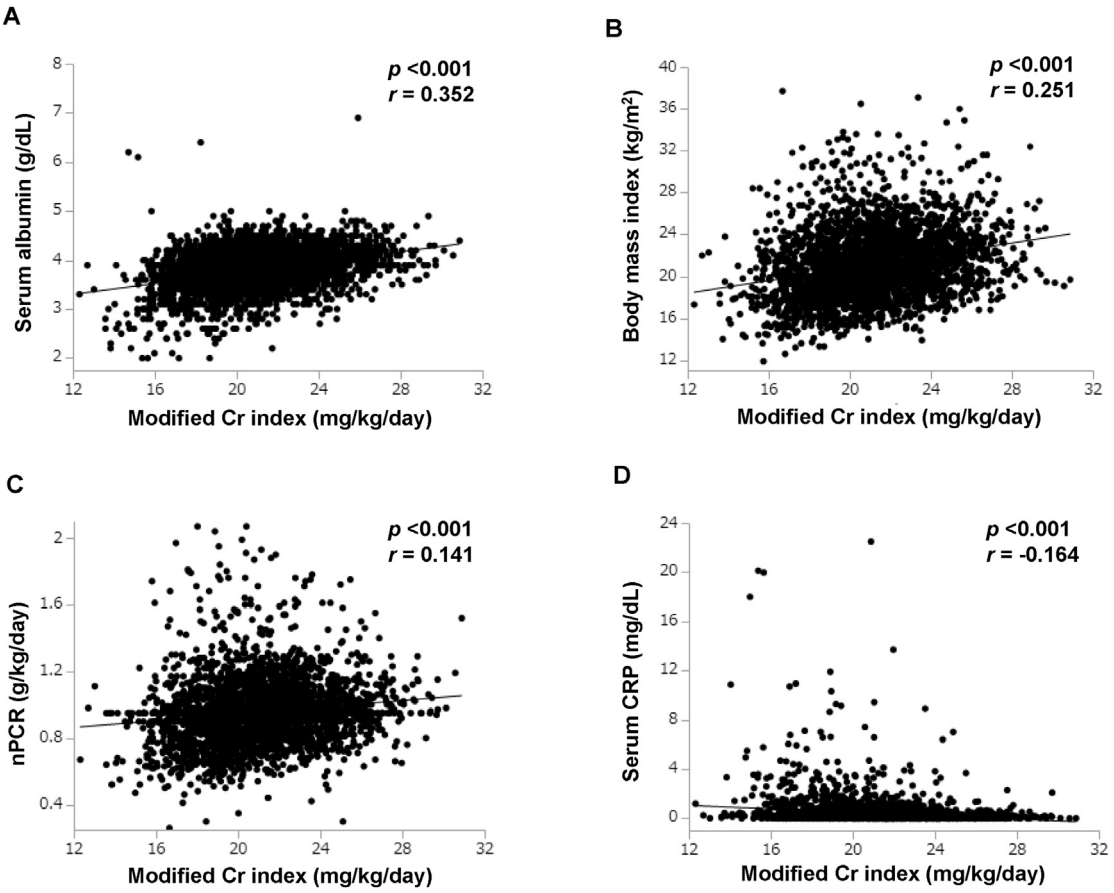

Fig. 1. Correlation between the modified Cr index and fundamental nutritional and inflammatory indicators.
Correlation between the modified Cr index and (A) serum albumin levels, (B) body mass index, (C) nPCR, and (D) serum CRP levels. Pearson's correlation coefficient was calculated for correlation between the modified Cr index and serum albumin levels, body mass index, and nPCR. Spearman's rank correlation coefficient was calculated for correlation between the modified Cr index and serum CRP levels. A two-tailed *p*-value less than 0.05 was considered statistically significant. Cr, creatinine; CRP, C-reactive protein; nPCR, normalized protein catabolic rate.

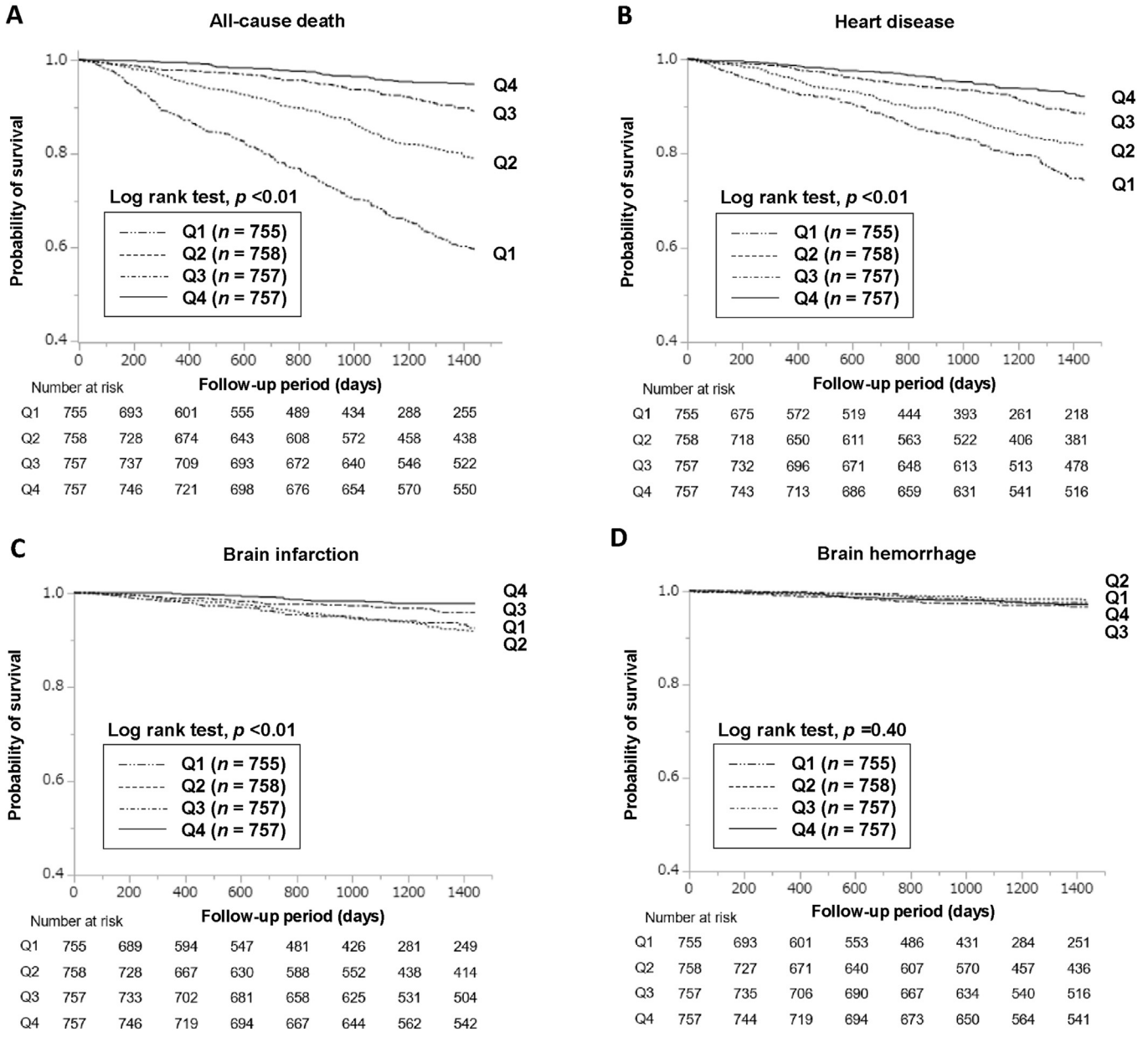

Fig. 2. Kaplan-Meier curves for the incidence of all-cause death, heart disease, brain infarction, and brain hemorrhage in each group stratified by sex-specific modified Cr index. (A) All-cause death, (B) heart disease, (C) brain infarction, and (D) brain hemorrhage. Patients were stratified into sex-specific quartiles according to the modified Cr index. Log rank test was used to analyze statistical differences. A two-tailed p value < 0.05 was considered statistically significant. Cr, creatinine; Q, quartile of the modified Cr index.

lowest modified Cr index quartile (Q1) showed a higher adjusted HR for the incidence rate of heart disease than did the reference group (Q4) (Table 2). The HR [95% CI] for a 1 mg/kg/day decrease in the modified Cr index was 1.13 (1.04–1.21, $p < 0.01$). In the unadjusted Cox proportional hazards model, patients with lower modified Cr index quartiles (Q1 and Q2) showed higher HRs for the incidence rate of brain infarction than did the reference group (Q4). However, after adjustment for potential confounding factors, the incidence rate of brain infarction was not significantly different among the four quartiles. The HR (95% CI) for a 1 mg/kg/day decrease in the modified Cr index was 0.99 (0.86–1.13, $p = 0.87$). In the unadjusted and multivariable-adjusted Cox proportional hazards models, the incidence rate of brain hemorrhage was not significantly different among the four quartiles. The HR (95% CI) for a 1 mg/kg/day decrease in the modified Cr index was 0.92 (0.76–1.12, $p = 0.41$). When all of the data were also analyzed by the Fine–Gray proportional subdistribution hazards model, a lower modified Cr index was still significantly associated with a higher incidence rate of heart disease, but was not significantly associated with the incidence rate of stroke (Table 2).

3.3. Non-linear association between the modified creatinine index and clinical outcomes

To determine a non-linear association between the modified Cr index and outcomes, we used multivariable-adjusted cubic spline curves. HRs for all-cause death and heart disease increased with a decrease in the modified Cr index. However, HRs for brain infarction and hemorrhage were not significantly associated with the modified Cr index (Fig. 3).

Table 2
Hazard ratios for outcomes in each group stratified by sex-specific modified creatinine index quartiles ($n = 3027$).

	Unadjusted model			Multivariable-adjusted model			Competing risk model		
	HR (95% CI)	*p*-value	*p* for trend	HR (95% CI)	*p*-value	*p* for trend	HR (95% CI)	*p*-value	*p* for trend
All-cause death			<0.001			<0.001			
Q1	9.99 (7.11–14.47)	<0.001		2.76 (1.75–4.43)	<0.001				
Q2	4.40 (3.08–6.48)	<0.001		1.97 (1.31–3.03)	<0.001				
Q3	2.13 (1.44–3.22)	<0.001		1.35 (0.90–2.08)	0.15				
Q4	1.00 (reference)	–		1.00 (reference)	–				
Every 1 mg/kg/day decrease in the modified Cr index	1.31 (1.27–1.36)	<0.001		1.19 (1.11–1.27)	<0.001				
Heart disease			<0.001			0.01			0.02
Q1	3.69 (2.69–5.14)	<0.001		1.68 (1.06–2.68)	0.03		1.62 (1.02–2.56)	0.04	
Q2	2.51 (1.82–3.52)	<0.001		1.41 (0.95–2.10)	0.09		1.45 (0.97–2.16)	0.07	
Q3	1.51 (1.06–2.16)	0.02		1.10 (0.76–1.62)	0.61		1.16 (0.80–1.68)	0.44	
Q4	1.00 (reference)	–		1.00 (reference)	–		1.00 (reference)	–	
Every 1 mg/kg/day decrease in the modified Cr index	1.14 (1.09–1.18)	<0.001		1.13 (1.04–1.21)	0.002		1.11 (1.03–1.19)	0.007	
Brain infarction			<0.001			0.38			0.18
Q1	3.49 (1.96–6.55)	<0.001		0.68 (0.30–1.59)	0.37		0.63 (0.30–1.29)	0.20	
Q2	3.63 (2.08–6.70)	<0.001		1.13 (0.57–2.32)	0.74		1.15 (0.59–2.22)	0.69	
Q3	1.85 (1.00–3.57)	0.049		0.92 (0.48–1.84)	0.82		0.96 (0.50–1.84)	0.91	
Q4	1.00 (reference)	–		1.00 (reference)	–		1.00 (reference)	–	
Every 1 mg/kg/day decrease in the modified Cr index	1.17 (1.10–1.25)	<0.001		0.99 (0.86–1.13)	0.87		0.96 (0.86–1.06)	0.40	
Brain hemorrhage			0.34			0.098			0.07
Q1	0.84 (0.40–1.72)	0.64		0.48 (0.16–1.46)	0.20		0.42 (0.13–1.38)	0.15	
Q2	0.70 (0.33–1.42)	0.32		0.43 (0.17–1.06)	0.07		0.42 (0.17–1.02)	0.06	
Q3	1.23 (0.67–2.29)	0.50		0.84 (0.42–1.70)	0.62		0.87 (0.41–1.82)	0.71	
Q4	1.00 (reference)	–		1.00 (reference)	–		1.00 (reference)	–	
Every 1 mg/kg/day decrease in the modified Cr index	0.95 (0.87–1.04)	0.27		0.92 (0.76–1.12)	0.41		0.90 (0.77–1.06)	0.22	

Unadjusted and multivariable adjusted HRs were analyzed by the Cox proportional hazards risk model and the Fine–Gray proportional subdistribution hazards model with all-cause death as a competing risk. The covariates included age, sex, the presence of diabetic nephropathy, history of cardiovascular events and bone fractures, dialysis vintage, dialysis time, systolic blood pressure, CTR, nPCR, Kt/V for urea, body mass index, blood hemoglobin, serum levels of albumin, total cholesterol, urea nitrogen, C-reactive protein, corrected calcium, phosphate, alkaline phosphatase, and parathyroid hormone, and use of erythropoiesis stimulating agents, anti-hypertensives, phosphate-binders and vitamin D receptor activators. A two-tailed *p*-value <0.05 was considered statistically significant.
CI, confidence interval; Cr, creatinine; HR, hazard ratio; Q, quartile of the modified Cr index.

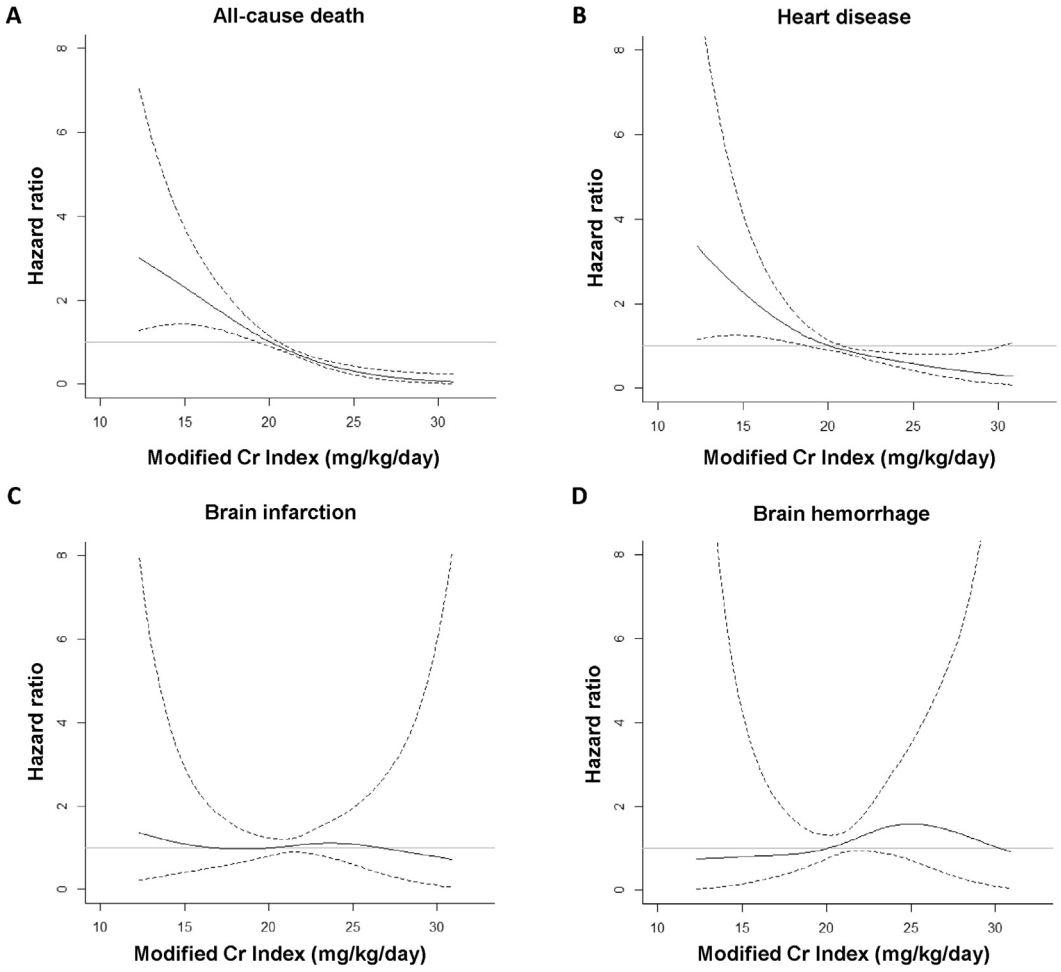

Fig. 3. Multivariable-adjusted restricted cubic spline plots of hazard ratio (HR) for (A) all-cause death, (B) heart disease, (C) brain infarction, and (D) brain hemorrhage according to the modified Cr index. Solid lines represent HR and dotted lines represent 95% confidence interval. The multivariable-adjusted model was adjusted for age, sex, presence of diabetic nephropathy, history of cardiovascular events and bone fractures, dialysis vintage, dialysis time, systolic blood pressure, cardiothoracic ratio, normalized protein catabolic rate, Kt/V for urea, body mass index, hemoglobin, serum levels of albumin, total cholesterol, urea nitrogen, C-reactive protein, corrected calcium, phosphate, alkaline phsophatase, and parathyroid hormone, and use of erythropoiesis stimulating agents, anti-hypertensives, phosphate-binders, and vitamin D receptor activators. Cr, creatinine.

4. Discussion

In this prospective cohort study of patients with prevalent HD, we showed that the modified Cr index was significantly correlated with known nutritional and inflammatory markers (serum levels of albumin and CRP, nPCR, and body mass index). Additionally, a lower modified Cr index was significantly associated with a higher incidence of heart disease and all-cause death, even after rigorous adjustment for potential confounding factors using the Cox proportional hazards model and the Fine–Gray proportional subdistribution hazards model. By contrast, we did not identify a relationship between the modified Cr index and the incidence of stroke. Our study suggested that decreased skeletal muscle mass, as shown by a lower modified Cr index, was associated with an increased risk for the incidence of heart disease and all-cause death in patients on HD.

Accumulating evidence has suggested that MICS and MIA are critical risk factors for cardiovascular events and all-cause mortality in patients on HD [28,29]. In a prospective cohort study of patients on HD, Combe et al. reported that hypoalbuminemia was significantly associated with a worse prognosis during the 2-year follow-up period [30]. Sueta et al. also reported that simultaneous presence of MIA factors, such as lower serum albumin levels, higher serum CRP levels, and a history of receiving invasive procedures for atherosclerotic disease, predicted higher mortality of patients on HD in a community-based, observational study [31]. In our study, the modified Cr index was well correlated with nutritional and inflammatory markers, and may serve as a comprehensive marker of MICS and MIA (Fig. 1). Furthermore, the modified Cr index was strongly associated with the incidence of heart disease and all-cause mortality. Taken together, our data suggest that the modified Cr index serves as a comprehensive surrogate index of MICS and MIA, as well as a surrogate of skeletal muscle mass. This index can also be a useful clinical marker for evaluating overall prognosis in patients on maintenance HD.

A potential explanation for the association between a lower modified Cr index and our clinical outcomes is a direct effect of skeletal muscle mass on heart disease and mortality. Myokines, which are humoral mediators produced by skeletal muscle, act on myokine receptors expressed in various organs, such as bone and blood vessels [32]. Several types of myokines affect the cardiovascular system [33,34]. Patients with greater skeletal muscle mass maintain sufficient secretion of myokines, which might have a protective effect on the cardiovascular system. Conversely, patients

with less skeletal muscle mass may have an increased risk for cardiovascular disease and all-cause mortality, as in the present study.

Importantly, we did not identify an association between the modified Cr index and the risk for stroke. This finding suggests that the contributions of malnutrition and inflammation to the pathogenesis of heart disease and stroke in patients on HD might be different. Atherosclerosis, which is promoted by inflammation [35,36], is a cause of heart disease and stroke [37,38]. However, for stroke, volume and blood pressure lability or routine use of anticoagulants during HD, which are unique to patients on HD and are determined independently of the patients' nutritional state, might have a strong effect on the development of stroke [39]. In our study population, such unique HD factors might have a greater effect on development of stroke than MICS and MIA. This may be the reason why we could not identify an association between decreased skeletal muscle mass and the incidence of stroke.

A strength of our study is its large-scale, prospective design, and wide-ranging inclusion criteria. Therefore, our results are expected to reflect the risk for clinical outcomes in a real-world HD population. To the best of our knowledge, this is the first large-scale, prospective cohort study showing an association between a modified Cr index and the incidence of clinically important outcomes in patients on HD. Furthermore, although the modified Cr index was originally created based on data in France [19], our study showed that the relationship between the modified Cr index and prognosis was consistent among Japanese patients on HD. This finding suggested that the modified Cr index can be used as a prognostic factor, regardless of patients' ethnic background.

Some limitations in our study should be noted. First, we measured the modified Cr index only once at baseline. Therefore, a future study that enables time-dependent analysis will provide a more robust association between skeletal muscle mass surrogates and outcomes. Second, we did not evaluate RRF. Because serum Cr levels are determined by RRF and adequacy of dialysis in patients on HD [40], pre-dialysis Cr levels of patients with a higher RRF tend to be lower than those of patients with a lower RRF. Consequently, skeletal muscle mass as determined by the modified Cr index in patients with a higher RRF might be underestimated. Nevertheless, patients with a shorter dialysis vintage are likely to have preserved RRF, and the time on dialysis was shortest in those with the lowest modified Cr index quartile (Q1). Therefore, missing data of RRF might not have had a significant effect on the association between the modified Cr index and outcomes that were examined in the current study. Third, we did not have detailed information on the type of heart disease, the anatomical location of brain hemorrhage, and mechanistic subtype of brain infarction. The effect of the modified Cr index on the subtype of these outcomes might be different. Fourth, because of the nature of the observational study, we are unable to conclude a causal relationship from our current observations. Finally, although we rigorously adjusted for baseline confounding factors, known and unknown residual confounding factors might lead to a null hypothesis. Despite all of these limitations, we believe that the current study will provide a better understanding of the association between skeletal muscle mass surrogates and important clinical outcomes in patients receiving maintenance HD.

In conclusion, our data suggest that decreased skeletal muscle mass, as shown by a lower modified Cr index, is significantly associated with higher risks for the incidence of heart disease and all-cause death, but not with a risk for the incidence of stroke in patients receiving maintenance HD. The modified Cr index is significantly correlated with known nutritional and inflammatory markers in patients on HD. MIA/MICS expressed by a lower modified Cr index might be part of the underlying cause of the observed increase in all-cause mortality and heart disease risk. Because skeletal muscle mass is a potential target of intervention in patients on HD, further studies are important for determining whether pharmacological treatment or instruction to patients to increase skeletal muscle mass actually decreases cardiovascular events and all-cause death.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Research idea and study design: HA, SY, MTa, and MTo; data acquisition: SY, RY, MTa, MTo and KT; data analysis interpretation: HA, SY, RY, MTa, MTo and NT; statistical analysis: HY, SY, and RY; supervision or mentorship: TN, KT and TK. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. TN takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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