Malnutrition-Inflammation Complex Syndrome and Bone Fractures and Cardiovascular Disease Events in Patients Undergoing Hemodialysis: The Q-Cohort Study

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Rationale & Objective: Malnutrition-inflammation complex syndrome (MICS) is common in patients receiving hemodialysis and increases the risks of morbidity and mortality. However, few studies have examined the overall impact of MICS on disorders of the bone-cardiovascular axis.

Study Design: Prospective, multicenter, observational cohort study.

Setting & Participants: A total of 3,030 patients receiving maintenance hemodialysis registered in the Q-Cohort Study.

Predictors: A newly developed score for MICS composed of elements chosen from 8 baseline parameters related to nutrition and inflammation by bootstrap resampling, multivariable-adjusted Cox proportional hazard risk analysis for all-cause mortality, and the risk prediction rule. β-coefficients of each element analyzed in the multivariable-adjusted model were used for the creation of the MICS score.

Outcomes: Bone fractures, cardiovascular disease events, and the composite outcome of bone fractures and cardiovascular disease events.

Analytical Approach: Cox proportional hazard regression and Fine-Gray proportional subdistribution hazards regression.

Results: During a median follow-up of 4 years, 140 patients developed bone fractures and 539 developed cardiovascular disease events. Age; serum levels of creatinine, albumin, and C-reactive protein; and body mass index were selected for the creation of the MICS score. The median (IQR) MICS score was 196 (181-212). The multivariable-adjusted Cox proportional hazard risk model and the competing risk model showed that a higher MICS score was incrementally associated with elevated risks of bone fractures, cardiovascular disease events, and the composite outcome; hazard risks (95% CIs) of fractures, cardiovascular disease events, and the composite outcome for each 10-point increase in the MICS score were 1.18 (1.01-1.38), 1.16 (1.07-1.26), and 1.15 (1.07-1.24), respectively.

Limitations: One-time measurement of the parameters used for the creation of the MICS score.

Conclusions: Malnutrition and inflammation represented by the MICS score were associated with increased risks of bone-cardiovascular axis disorders in patients receiving maintenance hemodialysis.

Patients receiving hemodialysis are at extremely high risk of bone fractures and cardiovascular disease (CVD) events.[1,2] Because bone fractures and CVD events increase the risks of morbidity, hospitalization, and mortality, both bone fractures and CVD events place huge public burdens on the hemodialysis population.[1,3] Evidence has increasingly shown that the bone and cardiovascular systems form a tight link, share humoral mediators, and develop and maintain interdependently.[3-6] Bone fractures and CVD events share risk factors, coexist in the same patients, and form a self-perpetuating cycle.[7] Therefore, there is a need to identify modifiable and shared risk factors for this recently recognized bone-cardiovascular axis.

Patients receiving hemodialysis commonly have malnutrition and inflammation, and these conditions are closely associated with increased risks of all-cause and cardiovascular mortality.[8,9] Basic studies have shown that malnutrition, inflammation, and oxidative stress in patients with uremia play critical roles in the pathogenesis of derangement in the cardiovascular system.[10,11] To emphasize the close link among malnutrition, inflammation, and atherosclerosis-related cardiovascular diseases or comorbid conditions, the terms "malnutrition-inflammation-atherosclerosis syndrome" and "malnutrition-inflammation complex syndrome (MICS)" have been proposed.[8,9,12] Although serum markers of inflammation and malnutrition are associated with increased risks of bone fractures and CVD events, single markers fail to demonstrate the overall impact on the derangement in the bone-cardiovascular axis in patients receiving hemodialysis.[13-17] Measurement of skeletal muscle mass by computed tomography, magnetic resonance imaging, dual-energy x-ray absorptiometry, or electrical bioimpedance analysis is another approach to evaluate nutritional status.[16] Furthermore, a combination of several nutrition-related surrogate markers has been used in patients receiving hemodialysis, including the geriatric nutritional risk index, creatinine (Cr) index, and malnutrition-inflammation score (MIS).[8,13,18-21] Importantly, some of these measures are subjective, semi-quantitative, and 1-sided, whereas others require special devices and experience and are expensive, not easily repeatable at the bedside, complex, and cumbersome,

PLAIN-LANGUAGE SUMMARY

To determine the overall impact of nutrition and inflammation on the bone-cardiovascular axis, we analyzed an existing dataset from a multicenter, prospective, observational study of patients in Japan undergoing hemodialysis. We developed a novel nutrition and inflammation scoring system and determined the association between each patient's score and their risk of bone fractures and cardiovascular disease events. The scoring system consisted of age; serum levels of creatinine, albumin, and C-reactive protein; and body mass index. Patients experiencing malnourishment and inflammation had a higher score, which was associated with greater risk of bone fractures and cardiovascular disease events. Thus, our findings indicate that effective malnutrition and inflammation intervention is necessary to prevent bone fractures and cardiovascular disease events in patients undergoing hemodialysis.

making them unsuitable for application for the daily assessment of nutritional and inflammatory status in a large population. Accordingly, there is an urgent need for the development of a screening tool for the assessment of the nutritional and inflammatory status of patients receiving hemodialysis that is simple, intuitive, objective, numeric, less expensive, repeatable at the bedside, applicable to a large population, and requires neither special devices nor experience.

The present study had 2 main aims. The first aim was to elucidate the overall impact of malnutrition and inflammation on the derangement in the bone-cardiovascular axis in patients receiving hemodialysis. The second aim was to develop an objective and multifaceted score for MICS that can be used for the overall evaluation of nutritional and inflammatory status in patients receiving hemodialysis. To achieve these aims, we analyzed the dataset in the Q-Cohort Study, a multicenter, prospective, observational study of patients receiving maintenance hemodialysis.[16,22,23]

METHODS

Design of the Q-Cohort Study and Study Participants

The present study used the dataset in the Q-Cohort Study, a multicenter, prospective, longitudinal, observational study designed to identify risk factors for morbidity and mortality in patients undergoing hemodialysis.[16,22,23] Briefly, the study population consisted of 3,598 outpatients aged ≥18 years who received regular hemodialysis therapy between December 2006 and December 2007 at 39 hemodialysis facilities in Japan. All patients were followed up until December 2010, unless they were lost to follow-up. Among the 3,598 patients, 127 patients were excluded

from the analyses because of missing outcome data, and 441 patients were excluded because of insufficient information about baseline characteristics and medications. A total of 3,030 patients were finally included in the present analyses. The study was conducted under the Ethics of Clinical Research (Declaration of Helsinki). The Kyushu University Hospital Institutional Review Board for Clinical Research approved the protocol (no. 20-31), which was registered in the clinical trial registry (University Hospital Medical Information Network, UMIN000000556). All patients provided written informed consent before participating in the study.

Outcomes and Exposure

The primary outcomes were bone fractures, CVD events, and the composite outcome of bone fractures and CVD events. The secondary outcome was all-cause mortality. The main exposure was the baseline MICS score, which was newly developed in the present study. Bone fractures were confirmed by radiological findings and clinical symptoms; not all patients with bone fractures required hospitalization. Asymptomatic vertebral fractures were not included. The CVD events included congestive heart failure requiring hospitalization, acute coronary syndrome (myocardial infarction with or without ST-segment elevation and unstable angina), and hemorrhagic and ischemic stroke. Arrhythmia requiring hospitalization and intervention for peripheral arterial disease were not included as CVD events in the present study. The CVD events were periodically assessed and confirmed by the central outcome review board members, who were representatives of the attending physicians at all dialysis facilities in the Q-Cohort Study.

Covariates and Biochemical Determination

The baseline characteristics and potential confounding factors were collected by reviewing the medical records. Routine biochemical parameters were measured with autoanalyzers using standard procedures. The details of the measurements and calculations used in the present study have been described elsewhere.[23-25]

Development, Internal Validation, and External Validation of the MICS Score

The MICS score was developed by applying the bootstrapping technique, risk prediction rule, and multivariable-adjusted Cox proportional hazard model for all-cause mortality. The details of the statistical methods followed during the process of development, internal validation, and external validation of the MICS score are described in Item S1.

Statistical Analyses

Continuous variables were described as median (interquartile range), whereas categorical variables were expressed as number (percentage). Patients were divided

into quartiles (Q1-Q4) based on the MICS score created in the present study. For comparison of the baseline characteristics across quartiles by the MICS score, trend analyses were performed using the Jonckheere-Terpstra test for continuous variables and the Cochran-Armitage test for categorical variables.

In the main analysis, we examined the association between the MICS score and the estimated risks of bone fractures, CVD events, and the composite outcome by using Cox proportional hazards models. Unadjusted and multivariable-adjusted models were used for the estimation of the hazard ratio (HR) and 95% confidence interval (CI). Multivariable-adjusted models included the following parameters as covariates: covariates 1 (age; sex; presence of diabetic nephropathy; history of cardiovascular disease events and bone fractures; hemodialysis vintage; hemodialysis time per session; Kt/V for urea; normalized protein catabolic rate; serum levels of urea nitrogen, cholesterol, corrected calcium, phosphate, alkaline phosphatase, and parathyroid hormone; and use of phosphate binders and vitamin D receptor activators) for bone fractures and covariates 2 (covariates 1 and cardiothoracic ratio, systolic blood pressure, blood hemoglobin level, and use of antihypertensives) for CVD events and the composite outcome. Additionally, the multivariable-adjusted nonlinear association between the MICS score and outcomes was plotted as HRs and 95% CIs, using restricted cubic spline curves with 4 knots and setting the median MICS score as the reference. As a sensitivity analysis, the Fine-Gray proportional subdistribution hazards models for the composite outcome by treating all-cause mortality as a competing risk were applied to consider potential competing risks.[26] Also, to determine the age-independent impact of the MICS on the outcomes, the association between the outcomes and a MICS score excluding age in the process of the score development were examined. Subgroup analysis by the baseline characteristics was also conducted by setting the MICS score as a continuous variable and expressing the risks for the composite outcome as HRs (95% CIs) for every 10-point increase in the MICS score.

A 2-tailed P value of <0.05 was considered statistically significant unless otherwise specified. For the interaction term, a P value of <0.1 was considered statistically significant. Statistical analyses were performed using the JMP version 14.2 software (SAS Institute Inc), R version 4.0.2 (http://cran.rproject.org), and SAS software, version 9.4 (SAS Institute).

RESULTS

Clinical Background Characteristics and Incidences of Outcomes

The clinical characteristics at baseline are summarized in Table 1. The median (interquartile range) of age was 64.4

Table 1. Baseline Characteristics of the Studied Population (N = 3,030)

Baseline Characteristics	Summary Data
Basic information	
Age, y	64.4 (56.1-72.9)
Sex (male), n (%)	1794 (59.2%)
Diabetic nephropathy, n (%)	871 (28.7%)
History of cardiovascular diseases, n (%)	1038 (34.3%)
History of bone fractures, n (%)	301 (9.9%)
Dialysis vintage, y	5.5 (2.1-11.7)
Dialysis time per session, h	5.0 (4.0-5.0)
Single-pool Kt/V for urea	1.56 (1.40-1.73)
Normalized protein catabolic rate, g/kg/d	0.95 (0.84-1.04)
Body mass index, kg/m²	20.8 (18.8-23.1)
Systolic blood pressure, mm Hg	153 (139-168)
Blood tests results	
Blood hemoglobin, g/dL	10.5 (9.8-11.3)
Serum albumin, g/dL	3.8 (3.6-4.1)
Serum total cholesterol, mg/dL	152 (130-178)
Serum C-reactive protein, mg/dL	0.13 (0.05-0.30)
Serum urea nitrogen, mg/dL	66 (56-76)
Serum creatinine, mg/dL	10.3 (8.4-12.0)
Albumin-corrected serum calcium, mg/dL	9.4 (8.9-9.9)
Serum phosphate, mg/dL	4.9 (4.2-5.7)
Serum alkaline phosphatase, U/L	232 (182-311)
Serum PTH (intact assay), pg/mL	102 (46-208)
Medications	
Use of antihypertensive drugs, n (%)	1936 (63.9%)
Use of phosphate binders, n (%)	2479 (81.8%)
Use of VDRAs, n (%)	2147 (70.9%)

Note: Baseline data are expressed as median (interquartile range) for continuous variables and number (percentage) for categorical variables. A 2-tailed P value of <0.05 was considered statistically significant. Conversion factors for units: serum calcium in mg/dL to mmol/L, ×0.2495; serum creatinine in mg/dL to μmol/L, ×88.4; serum urea nitrogen in mg/dL to μmol/L, ×0.357; serum phosphate in mg/dL to mmol/L, ×0.3229; serum total cholesterol in mg/dL to mmol/L, ×0.02586.
Abbreviations: PTH, parathyroid hormone; VDRA, vitamin D receptor activator.

(56.1-72.9) years, 59.2% of patients were men, and 28.7% had diabetic nephropathy as the primary kidney disease. During a median observation period of 4 years, 140 (4.6%) patients developed bone fractures, 539 (17.8%) developed CVD events, 645 (21.3%) developed the composite outcome of bone fractures and CVD events, and 499 (16.5%) died of any cause.

Development, Internal Validation, and External Validation of the MICS Score

The detailed process of development, internal validation, and external validation of the MICS score is described in Tables S1-S3 and Figs S1-S6. Briefly, the final selected components of the MICS score were age; body mass index (BMI); and serum levels of albumin, Cr, and C-reactive protein (CRP). The nomogram used to calculate the MICS score for each patient was created by applying the risk prediction rule for all-cause mortality and is shown in Fig 1. The distribution of the MICS score is shown in Fig 2.
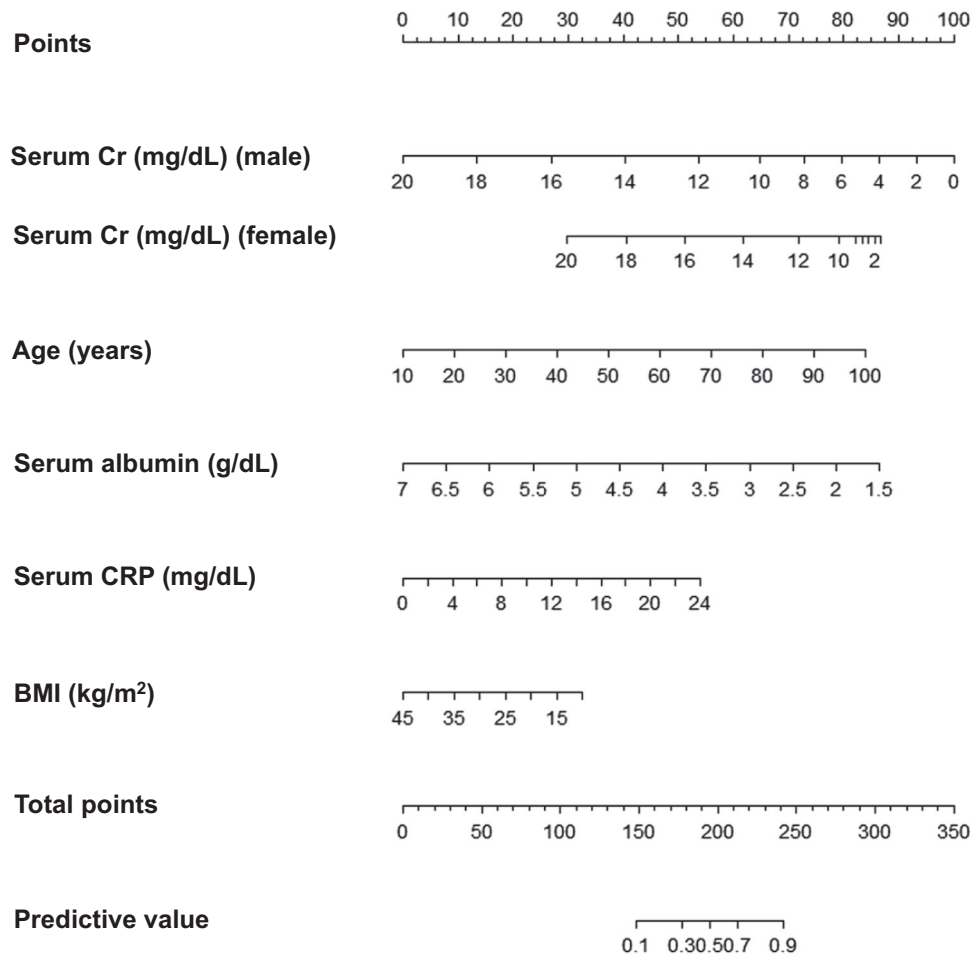
Figure 1. Nomogram to calculate the malnutrition-inflammation complex syndrome score based on the risk prediction rule. Abbreviations: BMI, body mass index; Cr, creatinine; CRP, C-reactive protein.

The median (interquartile range) of the MICS score was 196 (181-212).

Baseline Characteristics in Each Group Stratified by the MICS Score

Table 2 shows the baseline characteristics of the 3,030 patients divided into quartiles based on the MICS score. Patients with a high MICS score were significantly older ($P < 0.05$), more likely to be men, had a significantly higher prevalence of diabetic nephropathy ($P < 0.05$), higher prevalence of a history of CVD events and bone fractures, shorter median dialysis history, shorter median dialysis time per session, and lower normalized protein catabolic rate and BMI. Patients with a higher MICS score had significantly lower blood hemoglobin levels and serum levels of albumin, total cholesterol, urea nitrogen, Cr, corrected calcium, phosphate, and parathyroid hormone ($P < 0.05$) and had significantly higher median serum CRP and alkaline phosphatase levels ($P < 0.05$). Phosphate binders and vitamin D receptor activators were less frequently used by patients with a higher MICS score.
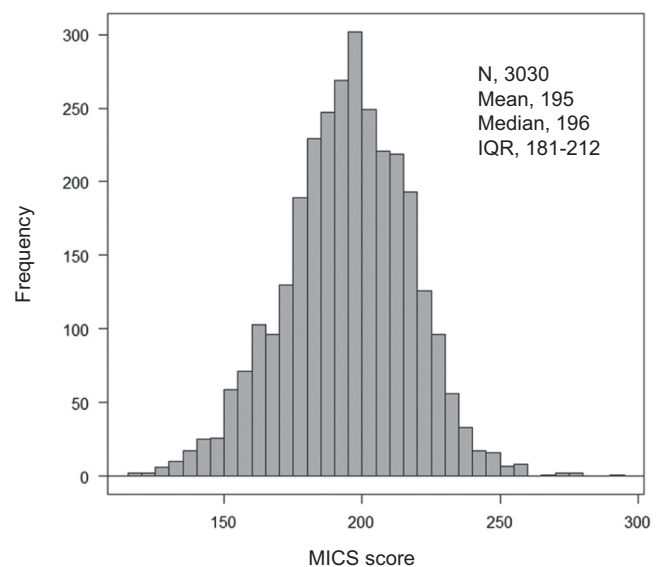

Figure 2. Distribution of the MICS score (N = 3,030). Abbreviations: IQR, interquartile range; MICS, malnutrition-inflammation complex syndrome; N, number.

Table 2. Baseline Characteristics in Each Quartile Based on the MICS Score at Baseline (N = 3,030)

| Baseline Characteristics | Quartiles Stratified by the Baseline MICS Score | | | | |
| | Q1: 116-181 | Q2: 182-196 | Q3: 197-211 | Q4: 212-294 | |
	n = 777	n = 753	n = 775	n = 725	P for Trend
Basic information					
Age, y	50.9 (43.0-57.0)	61.0 (56.9-65.8)	68.5 (63.9-73.2)	77.4 (71.9-81.9)	<0.001
Sex (male), n (%)	422 (54.3%)	439 (58.3%)	495 (63.9%)	438 (60.4%)	0.002
Diabetic nephropathy, n (%)	130 (16.7%)	234 (31.1%)	278 (35.9%)	229 (31.6%)	<0.001
History of cardiovascular diseases, n (%)	136 (17.5%)	252 (33.5%)	307 (39.6%)	343 (47.3%)	<0.001
History of bone fractures, n (%)	39 (5.0%)	54 (7.2%)	78 (10.1%)	130 (17.9%)	<0.001
Dialysis vintage, y	7.2 (3.5-13.2)	6.7 (2.6-13.1)	4.6 (1.8-10.8)	3.8 (1.2-8.7)	<0.001
Dialysis time per session, h	5.0 (4.5-5.0)	5.0 (4.5-5.0)	5.0 (4.0-5.0)	4.5 (4.0-5.0)	<0.001
Single-pool Kt/V for urea	1.56 (1.40-1.75)	1.56 (1.39-1.73)	1.56 (1.42-1.72)	1.56 (1.42-1.73)	0.69
Normalized protein catabolic rate, g/kg/d	0.97 (0.90-1.08)	0.95 (0.85-1.05)	0.95 (0.84-1.04)	0.90 (0.78-0.98)	<0.001
Body mass index, kg/m²	21.7 (19.5-24.0)	21.5 (19.4-23.6)	20.8 (19.1-23.1)	19.4 (17.8-21.3)	<0.001
Cardiothoracic ratio	48.6 (45.9-51.8)	50.0 (47.0-53.2)	50.6 (47.3-54.2)	52.2 (48.2-56.3)	<0.001
Systolic blood pressure, mm Hg	152 (136-167)	154 (140-169)	154 (140-168)	152 (136-168)	0.53
Blood tests results					
Blood hemoglobin, g/dL	10.6 (10.0-11.4)	10.7 (10.0-11.4)	10.5 (9.8-11.2)	10.3 (9.5-11.0)	<0.001
Serum albumin, g/dL	4.1 (3.9-4.3)	3.9 (3.7-4.1)	3.8 (3.6-4.0)	3.4 (3.2-3.7)	<0.001
Serum total cholesterol, mg/dL	155 (133-182)	153 (133-182)	153 (131-179)	146 (124-167)	<0.001
Serum C-reactive protein, mg/dL	0.10 (0.03-0.20)	0.13 (0.05-0.24)	0.13 (0.07-0.30)	0.22 (0.10-0.80)	<0.001
Serum urea nitrogen, mg/dL	72 (63-82)	68 (59-77)	65 (56-74)	60 (50-69)	<0.001
Serum creatinine, mg/dL	12.6 (10.9-14.3)	10.8 (9.4-12.1)	9.5 (8.2-11.1)	8.0 (6.7-9.3)	<0.001
Albumin-corrected serum calcium, mg/dL	9.4 (8.9-9.9)	9.5 (8.9-9.9)	9.3 (8.8-9.8)	9.3 (8.9-9.8)	0.010
Serum phosphate, mg/dL	5.3 (4.5-6.1)	5.0 (4.4-5.8)	4.8 (4.1-5.5)	4.4 (3.8-5.2)	<0.001
Serum alkaline phosphatase, U/L	206 (161-277)	229 (180-313)	239 (185-308)	260 (211-345)	<0.001
Serum PTH (intact assay), pg/mL	119 (55-243)	108 (49-216)	105 (49-212)	83 (39-159)	<0.001
Medications					
Use of antihypertensive drugs, n (%)	477 (61.4%)	506 (67.2%)	498 (64.3%)	455 (62.8%)	0.84
Use of phosphate binders, n (%)	715 (92.0%)	666 (88.4%)	625 (80.6%)	473 (65.2%)	<0.001
Use of VDRAs, n (%)	586 (75.4%)	540 (71.7%)	560 (72.3%)	461 (63.6%)	<0.001

Note: Baseline data are expressed as median (interquartile range) for continuous variables and number (percentage) for categorical variables. The Cochran-Armitage test was used to determine *P* values for trends of categorical variables, whereas the Jonckheere-Terpstra test was used to determine *P* values for trends of continuous variables. A 2-tailed *P* value of <0.05 was considered statistically significant. Conversion factors for units: serum calcium in mg/dL to mmol/L, ×0.2495; serum creatinine in mg/dL to μmol/L, ×88.4; serum urea nitrogen in mg/dL to μmol/L, ×0.357; serum phosphate in mg/dL to mmol/L, ×0.3229; serum total cholesterol in mg/dL to mmol/L, ×0.02586.
Abbreviations: MICS, malnutrition-inflammation complex syndrome; PTH, parathyroid hormone; Q, quartile by the MICS score; VDRA, vitamin D receptor activator.

Incidences of Outcomes in Each Quartile Based on the MICS Score

The numbers of patients who developed bone fractures, CVD events, and the composite outcome in the 4 groups stratified by the MICS score are shown in Table 3. Patients with a higher MICS score showed significantly higher incidences of bone fractures, CVD events, and the composite outcome (P < 0.05).

Association Between the MICS Score and the Risks of Bone Fractures, CVD Events, and the Composite Outcome

Figure 3 shows the unadjusted Kaplan-Meier curves for bone fractures, CVD events, and the composite outcome in patients grouped into quartiles based on the MICS score. Patients with a higher MICS score showed a lower event-free survival than those with a lower MICS score (log-rank P value < 0.05). The multivariable-adjusted Cox proportional hazard risk model analysis showed that the risks for bone fractures, CVD events, and the composite outcome significantly and incrementally increased in tandem with the MICS score (Table 4). Similar results were obtained even when the MICS score was treated as a continuous variable and the risks for these outcomes were evaluated by every 10-point increase in the MICS score: 1.18 (1.01-1.38), 1.16 (1.07-1.26), and 1.15 (1.07-1.24), respectively (Table 4). Furthermore, restricted cubic spline curve analyses also showed that a higher MICS score was marginally associated with increased risks of bone fractures and significantly associated with increased risks of CVD events and composite outcome (Fig 4).

Notably, even taking the competing risk of all-cause mortality into account, the association between the MICS score and the risk of the composite outcome remained statistically significant (Table 5). The multivariable-adjusted HR (95% CI) for every 10-point increase in the MICS score was 1.16 (1.07-1.25) (P < 0.001).

Table 3. Number of Events in Each Quartile Based on the MICS Score (N = 3,030)

	Total (N = 3,030)	Quartiles Based on the MICS Score				P for Trend
		Q1: 116-181 (n = 777)	Q2: 182-196 (n = 753)	Q3: 197-211 (n = 775)	Q4: 212-294 (n = 725)	
Bone fractures	140 (4.6%)	19 (2.5%)	35 (4.7%)	41 (5.3%)	45 (6.2%)	<0.001
CVD events	539 (17.8%)	69 (8.9%)	123 (16.3%)	162 (20.9%)	185 (25.5%)	<0.001
Composite outcome	645 (21.3%)	87 (11.2%)	150 (19.9%)	189 (24.4%)	219 (30.2%)	<0.001
All-cause death	499 (16.5%)	24 (3.1%)	74 (9.8%)	137 (17.7%)	264 (36.4%)	<0.001

Note: Data are expressed as number (percentage) in each group. The Cochran-Armitage test was used to determine *P* values for trends of categorical variables. In the analysis of the composite outcome, the first event was counted when the same patients developed both bone fractures and CVD events during the observation period. A *P* value of <0.05 was considered statistically significant.
Abbreviations: CVD, cardiovascular disease; MICS, malnutrition-inflammation complex syndrome; Q, quartile by the MICS score.
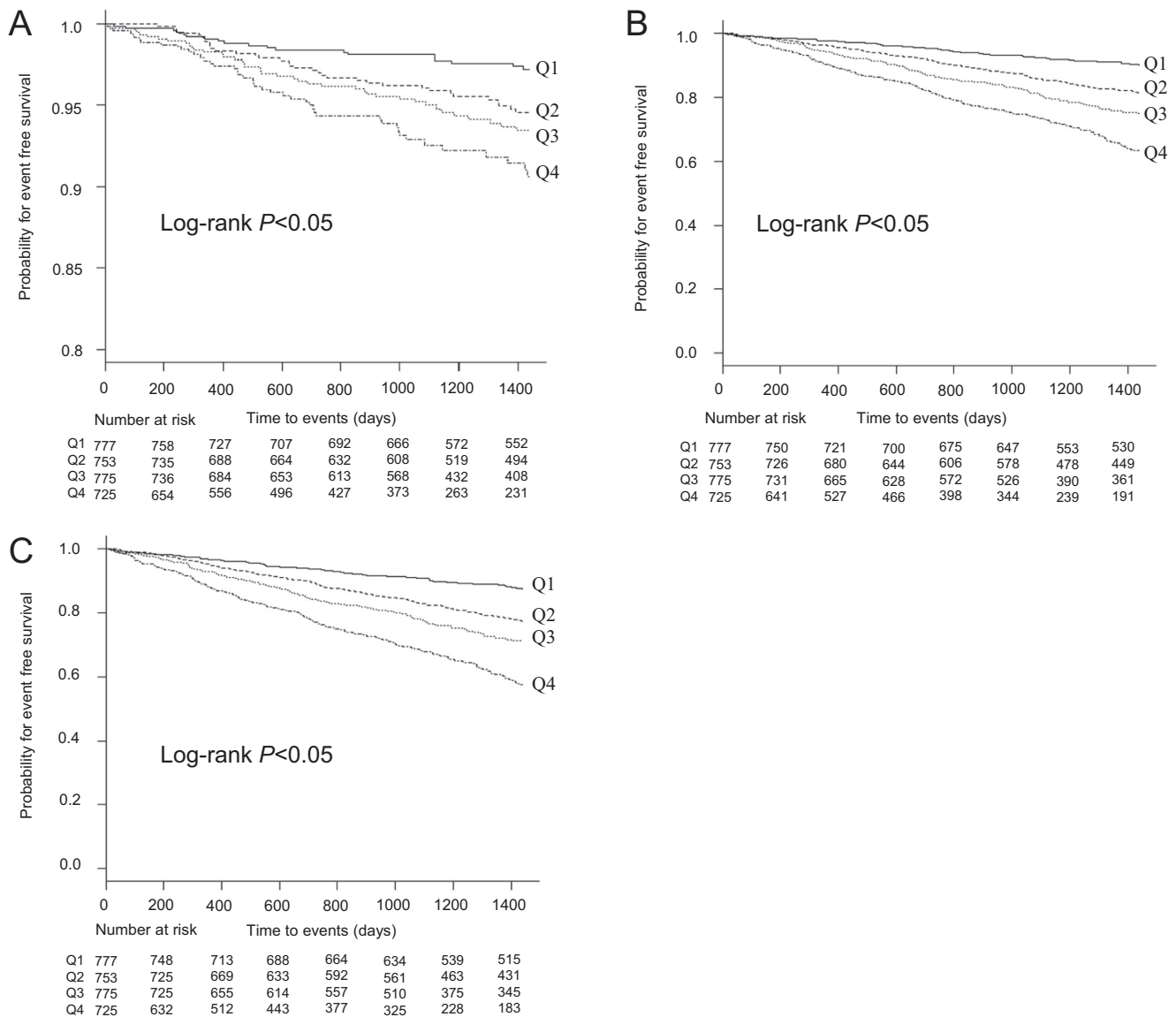

Figure 3. Unadjusted Kaplan-Meier analyses for the outcomes among patients stratified by the MICS score quartiles. (A) Bone fractures. (B) CVD events. (C) Composite outcome. Log-rank test was used to determine the statistical significance. A 2-tailed *P* value of <0.05 was considered statistically significant. Abbreviations: CVD, cardiovascular disease; MICS, malnutrition-inflammation complex syndrome.

Table 4. Association Between the MICS Score and Outcomes Analyzed by the Cox Proportional Hazard Risk Model (N = 3,030)

Outcomes	Unadjusted Model			Multivariable-adjusted Model		
	HR (95% CI)	*P* Value	*P* for Trend	HR (95% CI)	*P* Value	*P* for Trend
Bone fractures						
Q1; 116-181	1 (reference)			1 (reference)		
Q2; 182-196	1.97 (1.13-3.44)	0.02	<0.001	1.53 (0.82-2.85)	0.17	0.05
Q3; 197-211	2.43 (1.41-4.18)	0.001		1.75 (0.87-3.53)	0.12	
Q4; 212-294	3.51 (2.05-6.00)	<0.001		2.40 (1.03-5.58)	0.04	
Every 10 score increase in the MICS score	1.24 (1.14-1.34)	<0.001		1.18 (1.01-1.38)	0.04	
CVD events						
Q1; 116-181	1 (reference)			1 (reference)		
Q2; 182-196	1.96 (1.46-2.63)	<0.001	<0.001	1.30 (0.94-1.81)	0.11	0.02
Q3; 197-211	2.76 (2.08-3.65)	<0.001		1.55 (1.08-2.23)	0.02	
Q4; 212-294	4.27 (3.24-5.64)	<0.001		1.98 (1.27-3.08)	0.002	
Every 10 score increase in the MICS score	1.28 (1.23-1.34)	<0.001		1.16 (1.07-1.26)	<0.001	
Composite outcome						
Q1; 116-181	1 (reference)			1 (reference)		
Q2; 182-196	1.89 (1.45-2.47)	<0.001	<0.001	1.30 (0.97-1.74)	0.08	<0.001
Q3; 197-211	2.57 (1.99-3.31)	<0.001		1.49 (1.07-2.07)	0.02	
Q4; 212-294	4.05 (3.16-5.20)	<0.001		1.97 (1.32-2.93)	<0.001	
Every 10 score increase in the MICS score	1.27 (1.23-1.32)	<0.001		1.15 (1.07-1.24)	0.002	

Note: Risk estimates are expressed as HR (95% CI). HRs were estimated by the Cox proportional hazard risk model using a conventional approach. In the multivariable-adjusted analysis for bone fractures, the covariates were age, sex, presence of diabetic nephropathy, history of cardiovascular disease events and bone fractures, hemodialysis vintage, hemodialysis time per session, Kt/V for urea, normalized protein catabolic rate, serum levels of urea nitrogen, total cholesterol, corrected calcium, phosphate, alkaline phosphatase, and parathyroid hormone, and use of phosphate binders and vitamin D receptor activators. In the multivariable-adjusted analysis for CVD events and the composite outcome, the covariates comprised the covariates in the bone fractures model plus the cardiothoracic ratio, systolic blood pressure, blood hemoglobin level, and use of antihypertensive drugs. A 2-tailed *P* value of <0.05 was considered statistically significant.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MICS, malnutrition-inflammation complex syndrome; Q, quartile based on the MICS score.

Effect Modifications by Baseline Characteristics Regarding the Association of the MICS Score With the Composite Outcome

When patients were divided into 2 groups based on the various baseline characteristics and the effect modifications were analyzed, the impact of the MICS score on the composite outcome was significantly augmented in patients without diabetic nephropathy as the primary kidney disease (P < 0.1). There were no significant interactions between the other baseline characteristics and the MICS score regarding the composite outcome (Fig 5).

Age-Independent Impact of the MICS Score on the Outcomes

To determine the age-independent impact of the nutritional and inflammatory statuses on the outcomes, we also developed a MICS score with age excluded as a potential component of the score development. In the development of the new MICS score without age, the parameters selected as components of the score were the serum levels of urea nitrogen, Cr, albumin, and CRP and the BMI. We then created another nomogram based on the same methods used in the creation of the age-included MICS score. When the MICS score without age was applied to the 3,030 patients undergoing hemodialysis, the MICS score

without age was marginally associated with an increased risk of bone fractures and significantly associated with elevated risks of CVD events and the composite outcome (Table S4). The multivariable-adjusted HR (95% CI) for these outcomes evaluated by every 10-point increase in the MICS score were 1.27 (1.04-1.55), 1.21 (1.09-1.34), and 1.19 (1.10-1.28), respectively.

DISCUSSION

Literature review suggests that both chronic inflammation and malnutrition are associated with the increased risks of morbidities. However, it remains unknown whether the bone-cardiovascular axis is disordered in patients receiving maintenance hemodialysis. In the present study, we demonstrated for the first time the overall impact of malnutrition and inflammation on the derangement in the bone-cardiovascular axis by developing a new score for MICS and analyzing the association between the MICS score and the risk of bone fractures, CVD events, and the composite outcome in patients receiving maintenance hemodialysis. The MICS score was composed of age; serum levels of Cr, albumin, and CRP; and BMI by applying the bootstrapping technique, risk prediction rule, and multivariable-adjusted Cox proportional hazard model for all-cause mortality. Our results suggest that patients
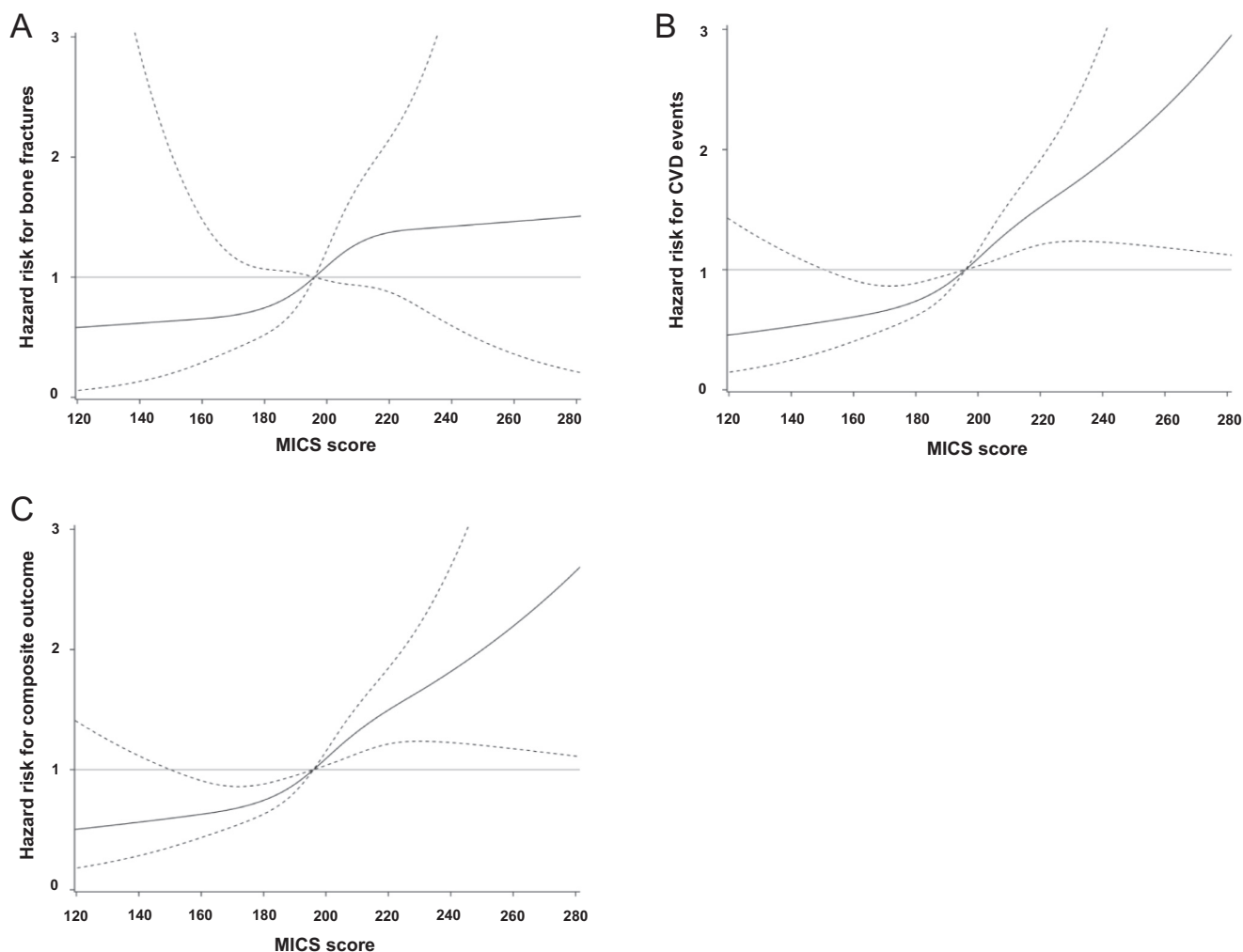
Figure 4. Multivariable-adjusted restricted cubic spline plots of hazard ratios (HRs) for the outcomes. (A) Bone fractures. (B) CVD events. (C) Composite outcome. Solid lines represent HRs, whereas dotted lines represent 95% confidence intervals. Horizontal gray lines correspond to the reference HR (1.0). The median MICS score of 196 was chosen as the reference value. Covariates used in the multivariable model are described in the Methods section. A 2-tailed *P* value of <0.05 was considered statistically significant. Abbreviations: CVD, cardiovascular disease; MICS, malnutrition-inflammation complex syndrome.

undergoing hemodialysis with a higher MICS score are at greater risk of derangement in the bone-cardiovascular axis, followed by increased incidences of CVD events and bone fractures, probably resulting in decreased activity of

daily living, reduced quality of life, and augmented risk of mortality.

The tight link between inflammation, malnutrition, and derangement of the bone-cardiovascular axis requires

Table 5. Association Between the MICS Score and Composite Outcome Analyzed by the Competing Risk Model (N = 3,030)

Outcomes	Unadjusted Model			Multivariable-adjusted Model		
Composite Outcome	HR (95% CI)	*P* Value	*P* for Trend	HR (95% CI)	*P* Value	*P* for Trend
Q1; 116-181	1 (reference)			1 (reference)		
Q2; 182-196	1.89 (1.45-2.47)	<0.001	<0.001	1.30 (0.97-1.74)	0.08	0.01
Q3; 197-211	2.57 (1.99-3.31)	<0.001		1.49 (1.08-2.06)	0.02	
Q4; 212-294	4.06 (3.16-5.21)	<0.001		1.97 (1.32-2.93)	<0.001	
Every 10 score increase in the MICS score	1.27 (1.23-1.32)	<0.001		1.16 (1.07-1.25)	<0.001	

Note: HRs and 95% CIs for the composite outcome were estimated by the Fine-Gray subdistribution hazard regression model by treating all-cause mortality as the competing risk. In the multivariable-adjusted analysis for the composite outcome, the covariates were age, sex, presence of diabetic nephropathy, history of cardiovascular disease events and bone fractures, hemodialysis vintage, hemodialysis time per session, Kt/V for urea, normalized protein catabolic rate, cardiothoracic ratio, systolic blood pressure, blood hemoglobin levels, serum levels of urea nitrogen, total cholesterol, corrected calcium, phosphate, alkaline phosphatase, and parathyroid hormone, and use of antihypertensive drugs, phosphate binders, and vitamin D receptor activators. A 2-tailed *P* value of <0.05 was considered statistically significant.
Abbreviations: CI, confidence interval; HR, hazard ratio; MICS, malnutrition-inflammation complex syndrome; Q, quartile based on the MICS score.
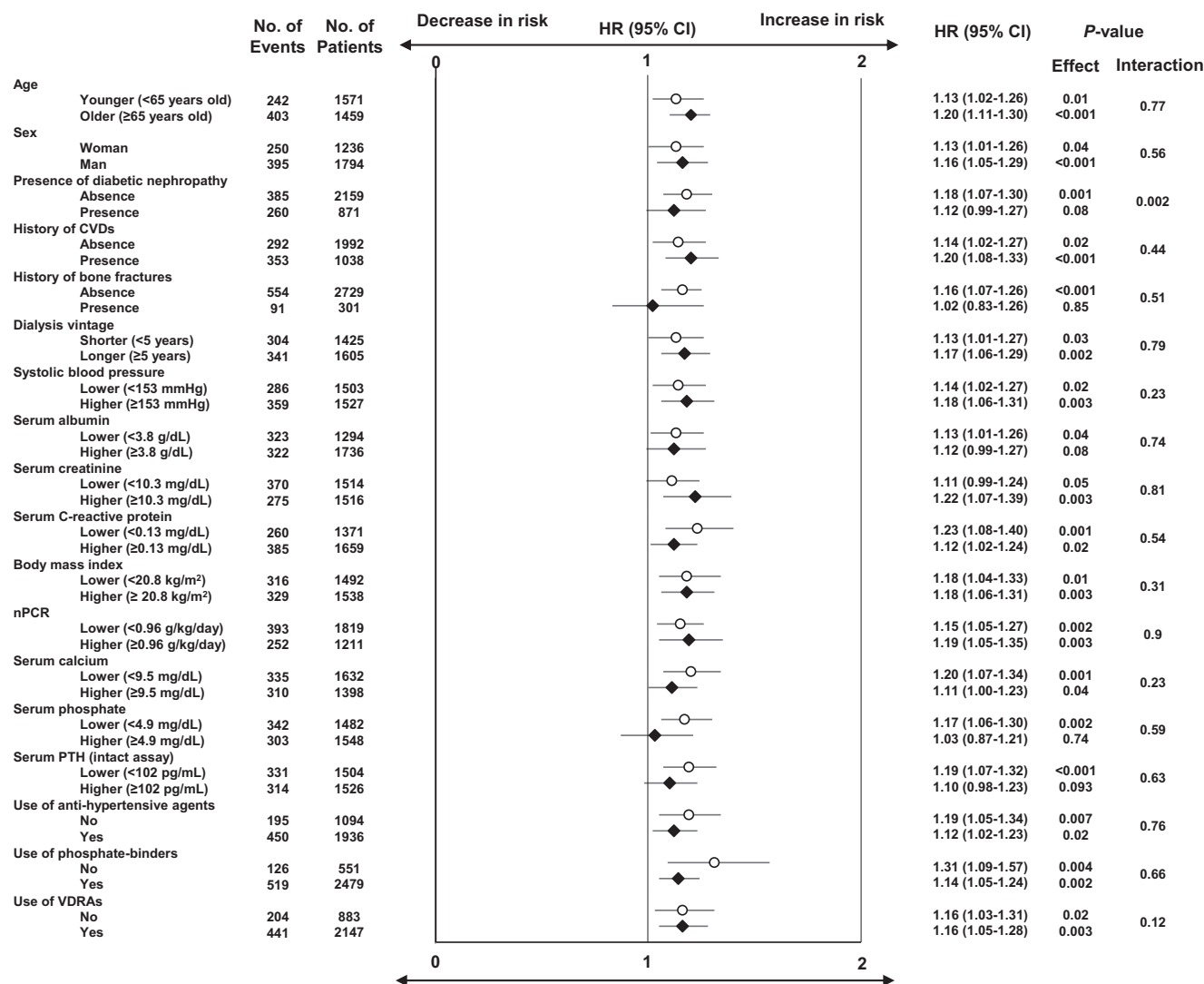
	No. of Events	No. of Patients	HR (95% CI)	HR (95% CI) Effect	P-value Interaction
Age					
Younger (<65 years old)	242	1571		1.13 (1.02-1.26)	0.01	0.77
Older (≥65 years old)	403	1459		1.20 (1.11-1.30)	<0.001	
Sex					
Woman	250	1236		1.13 (1.01-1.26)	0.04	0.56
Man	395	1794		1.16 (1.05-1.29)	<0.001	
Presence of diabetic nephropathy					
Absence	385	2159		1.18 (1.07-1.30)	0.001	0.002
Presence	260	871		1.12 (0.99-1.27)	0.08	
History of CVDs					
Absence	292	1992		1.14 (1.02-1.27)	0.02	0.44
Presence	353	1038		1.20 (1.08-1.33)	<0.001	
History of bone fractures					
Absence	554	2729		1.16 (1.07-1.26)	<0.001	0.51
Presence	91	301		1.02 (0.83-1.26)	0.85	
Dialysis vintage					
Shorter (<5 years)	304	1425		1.13 (1.01-1.27)	0.03	0.79
Longer (≥5 years)	341	1605		1.17 (1.06-1.29)	0.002	
Systolic blood pressure					
Lower (<153 mmHg)	286	1503		1.14 (1.02-1.27)	0.02	0.23
Higher (≥153 mmHg)	359	1527		1.18 (1.06-1.31)	0.003	
Serum albumin					
Lower (<3.8 g/dL)	323	1294		1.13 (1.01-1.26)	0.04	0.74
Higher (≥3.8 g/dL)	322	1736		1.12 (0.99-1.27)	0.08	
Serum creatinine					
Lower (<10.3 mg/dL)	370	1514		1.11 (0.99-1.24)	0.05	0.81
Higher (≥10.3 mg/dL)	275	1516		1.22 (1.07-1.39)	0.003	
Serum C-reactive protein					
Lower (<0.13 mg/dL)	260	1371		1.23 (1.08-1.40)	0.001	0.54
Higher (≥0.13 mg/dL)	385	1659		1.12 (1.02-1.24)	0.02	
Body mass index					
Lower (<20.8 kg/m²)	316	1492		1.18 (1.04-1.33)	0.01	0.31
Higher (≥ 20.8 kg/m²)	329	1538		1.18 (1.06-1.31)	0.003	
nPCR					
Lower (<0.96 g/kg/day)	393	1819		1.15 (1.05-1.27)	0.002	0.9
Higher (≥0.96 g/kg/day)	252	1211		1.19 (1.05-1.35)	0.003	
Serum calcium					
Lower (<9.5 mg/dL)	335	1632		1.20 (1.07-1.34)	0.001	0.23
Higher (≥9.5 mg/dL)	310	1398		1.11 (1.00-1.23)	0.04	
Serum phosphate					
Lower (<4.9 mg/dL)	342	1482		1.17 (1.06-1.30)	0.002	0.59
Higher (≥4.9 mg/dL)	303	1548		1.03 (0.87-1.21)	0.74	
Serum PTH (intact assay)					
Lower (<102 pg/mL)	331	1504		1.19 (1.07-1.32)	<0.001	0.63
Higher (≥102 pg/mL)	314	1526		1.10 (0.98-1.23)	0.093	
Use of anti-hypertensive agents					
No	195	1094		1.19 (1.05-1.34)	0.007	0.76
Yes	450	1936		1.12 (1.02-1.23)	0.02	
Use of phosphate-binders					
No	126	551		1.31 (1.09-1.57)	0.004	0.66
Yes	519	2479		1.14 (1.05-1.24)	0.002	
Use of VDRAs					
No	204	883		1.16 (1.03-1.31)	0.02	0.12
Yes	441	2147		1.16 (1.05-1.28)	0.003	

Figure 5. Effect modification by the baseline characteristics and medications regarding the association between the MICS score and the composite outcome. The composite outcome included bone fractures and CVD events. The median values or clinically relevant values were used for the cutoff values of the continuous variable. The HRs and 95% CIs for each 10-point increase in the MICS score were described. Cox proportional hazard regression analyses with the multivariable adjustment were performed for each baseline characteristic. Covariates included age, sex, presence of diabetic nephropathy, history of CVDs and bone fractures, dialysis vintage, dialysis time per session, Kt/V fore urea, normalized protein catabolic rate, cardiothoracic ratio, systolic blood pressure, blood hemoglobin levels, serum levels of urea nitrogen, total cholesterol, corrected calcium, phosphate, parathyroid hormone, alkaline phosphatase, and use of antihypertensive drugs, phosphate binders, and VDRAs. A 2-tailed P value of <0.05 was considered statistically significant. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MICS, malnutrition-inflammation complex syndrome; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; VDRA, vitamin D receptor activator.

elucidation. One reasonable mechanistic explanation for the observed associations may be that the risk factors for bone fractures and CVD events are shared in the bone-cardiovascular axis. Indeed, epidemiologic studies have shown that aging, hypertension, dyslipidemia, diabetes mellitus, oxidative stress, inflammation, and uremic milieu collectively accelerate the development and progression of osteoporosis and atherosclerosis/arteriosclerosis in chronic kidney disease.[3-7,27,28] In particular, inflammatory cytokines, including interleukin 1, interleukin 6, and tumor necrosis factor α, decrease bone strength by accelerating bone resorption and promoting atherosclerosis and arteriosclerosis.[29-31] Furthermore, malnutrition increases the risk of bone fractures through sarcopenia and deficiencies of vitamin D and protein and promotes CVD events via altered cellular metabolism in hemodialysis. We have recently shown that patients with decreased skeletal muscle mass and those with decreased protein intake have increased risks of bone fractures and CVD events.[16,32,33] These results indicate the importance of managing shared risk factors to prevent bone fractures and CVD events in patients undergoing hemodialysis.

Another explanation may be that the health of the bone and cardiovascular systems is interdependent and that degraded bone health promotes cardiovascular diseases, whereas damaged cardiovascular organs impair bone strength and quality via shared humoral mediators; this phenomenon has recently been called the bone-cardiovascular axis.[3-7] For example, osteoprotegerin, a decoy receptor of the receptor activator of nuclear kappa ligand, is expressed and secreted by the vascular cells and affects bone remodeling.[34] The C-type natriuretic peptide is excreted from endothelial cells and has an impact on bone cells.[35] In turn, the bone-forming cells excrete a variety of mediators (including calciprotein particles, sclerostin, and fibroblast growth factor 23), which act on vascular cells and alter the pathophysiology of atherosclerosis and arteriosclerosis.[36-38] These results suggest that the health of the bone and cardiovascular systems is partly maintained through humoral mediators. In addition, bone volume is regulated by the blood supply, and arteriosclerosis causes ischemic osteopathy in patients with advanced peripheral artery disease. Further studies are necessary to determine whether interventions for malnutrition or treatment for inflammation reduce the risk of bone fractures and CVD events and to develop effective dietary and pharmacological approaches for the prevention of the derangement in the bone-cardiovascular axis in patients receiving hemodialysis.

The newly developed MICS score was composed of 5 elements: age; serum levels of albumin, Cr, and CRP; and BMI. The definition of protein-energy wasting proposed by the International Society for Renal Nutrition and Metabolism includes the following categories: serum biochemistry, body mass, muscle mass, and dietary protein intake.[39] Our MICS score covered 3 of these 4 categories, indicating that the MICS score was consistent with the global guidelines. The new MICS score also included serum CRP level as a marker of inflammatory status. The serum CRP level provides different information than the serum albumin level and might increase the sensitivity for MICS detection.[40] Importantly, our MICS score correlated well with the geriatric nutritional risk index and Cr index (Fig S5), which are pre-established nutritional indexes used worldwide.[16,20] Furthermore, the internal and external validities of the MICS score were acceptably high (Figs S4 and S6). These results suggest that the MICS score could be useful for the assessment of nutritional and inflammatory status in patients receiving hemodialysis and for the prediction of clinically relevant outcomes. However, because aging is closely related to the development of both malnutrition and clinically relevant outcomes (including bone fractures and CVD events), the current MICS score that included age as a component may overestimate the association of malnutrition and inflammation with the outcomes. Notably, based on our sensitivity analysis, even when age was excluded from the MICS score, the age-independent MICS score was significantly correlated with increased risks of bone fractures, CVD

events, and the composite endpoint (Table S4). These results suggest that malnutrition and inflammation are associated with the derangement of the bone-cardiovascular axis independently of age in patients undergoing hemodialysis.

Although the MIS is a more comprehensive tool to evaluate MICS and is regarded as the gold standard, some of the parameters used in the MIS (such as the subjective global assessment) are subjective and thus yield large interobserver differences; furthermore, the MIS requires the serum transferrin level, which is not routinely measured in the daily management of the hemodialysis population.[8,21] Importantly, the selection of each component of the MIS is based on the clinical experience, whereas the components of our MICS score were determined using a scientific approach; furthermore, the cutoff values of each of the 10 components in the MIS are not based on the relative impact of each component on the nutritional status or other outcomes, although the MIS has been consequently associated with various clinically important outcomes in patients undergoing hemodialysis. In contrast, our MICS score requires age, BMI, and serum markers routinely measured in the clinical setting. In addition, the MICS score appears to be more objective than the MIS and provides a relatively high reproducibility. Indeed, the advocator of the MIS has mentioned that the MIS is not always the gold standard for the assessment of malnutrition and inflammation.[41] Furthermore, we have confirmed that the discriminative performance and calibration of the newly developed MICS score were acceptable. Overall, these findings suggest that our MICS score may help to stratify the risk of various outcomes in the hemodialysis population. In future studies, our MICS score should be compared with the MIS regarding the predictability of various clinically relevant outcomes in patients undergoing hemodialysis.

In the subgroup analysis, the impact of the MICS score on the composite outcome was augmented in patients without diabetic nephropathy. Because diabetes mellitus has been shown to accelerate the deterioration in the bone and cardiovascular system by hyperglycemia, advanced glycation endproducts, and increased oxidative stress and inflammation, the impact of malnutrition on the bone-cardiovascular axis may be relatively weakened in patients with diabetic nephropathy.[42,43] The potential interaction between diabetes mellitus and the MICS score regarding the bone-cardiovascular axis requires further examination in future studies.

The strengths of our study were its relatively large sample size, long observational period, and multivariable adjustment with a variety of baseline data, including medication. The present study had several limitations. First, because there is no gold standard measure to allocate a patient into a binary variable reflecting whether they are well-nourished or malnourished, we regressed the potential candidate parameters that were reportedly associated with nutritional status and inflammation to all-cause

mortality. Second, we assessed the status of malnutrition and inflammation only at the baseline. Because the nutritional status changed during the observation period, we were unable to eliminate the possibility of misclassification bias. Third, because the current study included prevalent patients undergoing hemodialysis rather than incident patients undergoing hemodialysis, the findings derived from our cohort might be affected by survivor bias.[44,45] Namely, patients with good nutritional status survived and were included in the cohort, and these patients had a longer dialysis vintage than those with malnutrition at baseline. However, even when patients were stratified by dialysis vintage, the associations between the MICS score and the outcomes were not altered. Fourth, because we had no available data to calculate the MIS, we could not compare the predictive performance between the MICS score and the MIS. Fifth, because of the observational nature of the study, we were unable to discuss the causality between the degree of malnutrition and inflammation and outcomes. Sixth, although we rigorously adjusted for confounding factors, we were unable to eliminate the possibility that the unmeasured and residual confounding factors might have biased the association observed in the present study. Hence, the results of the current study should be cautiously interpreted and require further confirmation in future well-designed studies.

In conclusion, we developed an objective score reflecting the concept of MICS in patients receiving hemodialysis and showed that malnutrition and inflammatory status determined by the MICS score was strongly associated with increased risks of bone fractures, CVD events, and the composite outcome in patients undergoing hemodialysis. Further studies are necessary to determine whether interventions for malnutrition and inflammation can decrease the incidence of events related to the deterioration of the bone-cardiovascular axis in patients receiving hemodialysis.

SUPPLEMENTARY MATERIAL

Supplementary File 1 (PDF)

Figure S1: The calculation formula for the risk prediction model of the MICS score.

Figure S2: Simplified scoring system for calculating the MICS score using multiple cutoff values.

Figure S3: Internal validation of the MICS score (n = 3,030).

Figure S4: External validation of the MICS score for the predictive performance and calibration using an independent hemodialysis cohort (n = 153).

Figure S5: Correlation between the MICS score and pre-established nutritional indexes. (A) Correlation between the MICS score and GNRI. (B) Correlation between the MICS score and Cr index. Pearson's correlation coefficients were calculated, and coefficients of determination (R^2) are described. A 2-tailed *P* value of <0.05 was considered statistically significant. Abbreviations: Cr, creatinine; GNRI, geriatric nutritional risk index; MICS, malnutrition-inflammation complex syndrome.

Figure S6: Comparison of the AUROCs for all-cause mortality among the models by the MICS score, GNRI, and Cr index (n = 3,030). (A) Comparison of the MICS score and GNRI. (B) Comparison of the MICS score and Cr index. A *P* value of <0.05 was considered statistically significant. The AUROC (= Harrel's C-statistics) was calculated by univariable Cox proportional hazard regression analysis with one of the nutritional parameters (MICS score, GNRI, or Cr index). Abbreviations: AUROC, area under the receiver operating characteristics curve; Cr, creatinine; GNRI, geriatric nutritional risk index; MICS, malnutrition-inflammation complex syndrome.

Item S1: Supplementary Patients and Methods.

Item S2: Supplementary Results.

Table S1: Frequencies of the Potential Candidate Parameters Chosen in the Process of the MICS Score Creation by Bootstrap Resampling and Cox Proportional Hazard Risk Analysis

Table S2: Baseline Characteristics of the Independent Hemodialysis Cohort (n = 153).

Table S3: Baseline Characteristics of the Independent Hemodialysis Cohort Stratified by Quartiles Based on the MICS Score (n = 153).

Table S4: Association Between the MICS Score Without Age and Outcomes Analyzed by the Cox Proportional Hazard Risk Model (n = 3,030).

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Are malnutrition and inflammation associated with an increased risk of fractures and cardiovascular disease?

Kidney Medicine

Methods and Cohort

Prospective, multicenter, observational cohort study

Japan

Patients receiving maintenance HD
N = 3,003

Dec 2006 – Dec 2007

Exposure

MICS score

	Q1: 116 – 181 n = 777	Q2: 182 – 196 n = 753	Q3: 197 – 211 n = 775	Q4: 212 – 294 n = 725	Every 10-score increase in the MICS score (HR, 95% CI)
Results					
Fractures	2.5%	4.6%	5.3%	6.2%	1.18 (1.01 – 1.38)
CVEs	8.9%	16.3%	20.9%	25.5%	1.16 (1.07 – 1.26)
Composite outcome	11.1%	18.9%	22.6%	28.7%	1.15 (1.07 – 1.24)
All-cause death	3.1%	9.8%	17.7%	36.4%	
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	

HD, hemodialysis; MICS, malnutrition–inflammation complex syndrome; Q, quartile by the MICS score; CVEs, cardiovascular disease events

Conclusion: Malnutrition and inflammation represented by the MICS score were associated with increased risks of bone-cardiovascular axis disorders in patients receiving maintenance hemodialysis.