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# Longitudinal effects of modified creatinine index on all-cause mortality in individuals receiving hemodialysis treatment

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**BACKGROUND:** The modified creatinine index (mCI), as a surrogate marker of muscle mass, has been associated with poor outcomes in patients undergoing hemodialysis. However, a single assessment may not reflect the clinical significance before an adverse clinical endpoint.

**OBJECTIVE:** Analyze mCI trajectories and their association with all-cause mortality in incident hemodialysis patients.

**DESIGN:** Retrospective observational cohort.

**SETTING:** Outpatient dialysis facility.

**PATIENTS AND METHODS:** We followed a cohort of patients who underwent maintenance hemodialysis treatment at least three times weekly for at least three months from 19 June 2010 to 29 December 2017. Clinical and laboratory features were measured at baseline. Longitudinal changes in the mCI were modeled using a joint longitudinal and survival model adjusted for baseline covariates and body mass index trajectories.

**MAIN OUTCOME MEASURE:** All-cause mortality.

**SAMPLE SIZE:** 408 with 208 males (50.7%).

**RESULTS:** The mean (SD) age was 62.2 (12.3) years. The mCI changes were evaluated for a median (interquartile range) follow-up of 2.16 (1.13, 3.73) years. Forty-six percent (n=188) of patients reached the endpoint. A steeper slope (per 0.1 unit increase in the decrease rate) in modified creatinine index was associated with increased risk of all-cause mortality (HR, 1.04; 95% CI, 1.02-1.07; *P*=.011). In addition, an annual 1 mg/kg/day decrease in modified creatinine index level increased the hazard of all-cause mortality by 4% (HR, 1.04; 95% CI, 1.02-1.07; *P*=.001).

**LIMITATIONS:** Residual kidney function was not observed in the data. Setting was single center and thus results may not be generalizable to other populations.

**CONCLUSION:** All-cause death was significantly associated with loss of muscle mass over time. Longitudinal trajectories of nutritional markers may predict the clinical outcomes in patients undergoing hemodialysis. This may also be valuable for individual risk stratification. Furthermore, early management may provide an opportunity to improve patient survival.

**CONFLICT OF INTEREST:** None.

Between the ages of 40 and 44 years, individuals with end-stage renal disease (ESRD) have shorter lifespans compared to the general population (more than 25-year difference in life expectancy for males and more than 30-year difference for females).[1] Studies have suggested that hemodialysis patients with higher body mass index (BMI) have a survival advantage.[2,3] However, prediction of mortality may be obscured using BMI because BMI does not distinguish lean body mass (LBM) from body fat.[4] Therefore, LBM might predict survival better than BMI or fat mass.[5,6]

The creatinine index might serve as a proxy of LBM.[7] A recent study showed that creatinine index correlates with muscle mass.[8] Other studies have shown that creatinine index relates to all-cause mortality in patients on hemodialysis,[9-11] but the data on the association between temporal evolutions of creatinine index and survival are limited. Determining the baseline exposure measurements or re-measuring the predictor during a first follow-up period only, e.g., not at routine intervals during longer-term follow-up, or using one repeated measure and describing the change between two measurements for prognosis, does not accurately represent the underlying temporal trajectory.[12-16] Therefore, the current study aimed to test the hypothesis that changes in creatinine index over time adjusted by BMI trajectories is independently associated with an increased risk of death among individuals receiving hemodialysis.

## PATIENTS AND METHODS
We conducted this retrospective cohort study of patients who received maintenance hemodialysis treatment at least three times per week for at least three calendar months at an outpatient dialysis facility at the University of Health Sciences, Kayseri City Education and Research Hospital, Division of Nephrology.. The first patient visit was the time of study onset, identified as the date of the first laboratory results and dialysis dose assessment. Individuals were observed in the facility at a frequency of at least once a month, depending on the patient's status. Patients were enrolled from 19 June 2010 to 29 December 2017, and were followed for up to 8 years or until the outcome event or censoring of data from loss to follow-up, transfer to another facility, initiation of renal transplantation, or until the end of the study on 1 January 2019. The analysis was performed using retrospective data from the hospital's electronic records and patient folders. The hospital institutional review board approved this study and waived the need for informed consent.

Patients had to be at least 18 years old and had baseline creatinine and BMI measurements. Patients were excluded if they withdrew from hemodialysis within 3 months of initiation.

### Outcome and primary predictor
The endpoint was all-cause mortality, which was defined as the period from the start of the study to death. The modified creatinine index (mCI) trajectory over time, which is a continuous surrogate measure of the LBM, was the primary predictor of interest. We calculated the mCI at baseline (first calendar quarter) and subsequent quarters using the following formula: Creatinine index (mg/kg/day)=16.21 + 1.12 × [1 if male; 0 if female] − 0.06 × age (years) − 0.08 × single pool Kt/V urea + 0.009 × serum creatinine before dialysis (μmol/L).[7] The initial (baseline) quarter for each patient was the calendar quarter in which the patient had been on dialysis for more than three months. Laboratory data collected within two days of the last dialysis session were used to determine mCI. BMI was determined by dividing the patient's post-hemodialysis weight (kg) by the square of his or her height, which was measured simultaneously with mCI.

### Covariates
The following variables were identified during the baseline period from medical record reviews: age, sex, dialysis vintage, primary kidney disease, and concomitant illnesses. Laboratory measurements included serum levels of hemoglobin, ferritin, creatinine, albumin, C-reactive protein (CRP), phosphorus, and parathyroid hormone (PTH). Age was based on age at the time of baseline assessment, with updated mCI calculations. The time between the start of hemodialysis and the date of censoring or death was described as dialysis vintage in each patient. The urea kinetic model was used to compute the single-pool Kt/V for urea as an indication of the dialysis dosage. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or a combination of hypertension diagnosis and antihypertensive drug usage. If antidiabetic prescriptions were administered, overnight fasting serum glucose was >126 mg/dL, HbA1C was >6.0 percent, and diabetes mellitus (DM) was appraised. Patients with a history of myocardial infarction, bypass surgery, coronary artery occlusion, heart failure, peripheral vascular disease, or cerebrovascular illness were considered to have cardiovascular disease (CVD).

### Statistical methods
Box plots and histograms were used to assess the distribution of continuous data. Near-normally distributed

continuous variables are reported as mean and standard deviation (SD), while non-normally distributed continuous variables are presented as medians and interquartile ranges. The chi-square test for categorical variables, a one-way ANOVA test for roughly normally distributed continuous data, and the Kruskal-Wallis test for skewed continuous variables were used to examine baseline differences between the groups. Since values for CRP, PTH, ferritin, and dialysis vintage were positively skewed, they were scaled using interquartile ranges (IQR) in all regression analyses, such that a 1-unit change corresponded to one IQR increase in value, and predictions were generated using these models. A natural scale was used to model the remaining variables. For analysis, individuals were divided into tertiles of mCI slope. A joint longitudinal survival model was used to examine the association between the mCI trend and the risk of mortality. The model analyzes the impact of a biomarker's rate of change on the risk of developing an event. The first derivative of the relationship between mCI trajectories and the hazard ratio of the clinical endpoint, which shows the relative change in the hazard of a clinical endpoint for a 0.1-unit increase in the change rate of mCI or a 1-unit increase in mCI per year, was the study's endpoint. These models have been thoroughly studied and reported in the literature.[17,18]

For illustration purposes, a fully adjusted linear mixed model was conducted separately from the joint models for predicting the mean trajectories of mCI. Models were repeated to estimate creatinine, mCI, and BMI slopes with adjustment for other baseline covariates. In addition, adjusted survival curves for all-cause mortality according to tertiles of slopes of mCI, which were estimated from joint models, were drawn using a fully adjusted Cox proportional hazard model as described by Therneau et al.[19] Analyses were first performed with mCI trajectories in a univariate joint model and then combined with BMI trajectories in a multivariate joint model. In both models, statistical adjustments with baseline variables were as follows: (i) crude model; (ii) plus age, sex, phosphorus, and PTH; (iii) plus hemoglobin, ferritin, dialysis vintage, and single-pool Kt/V (iv) plus baseline BMI, albumin, and CRP; and (v) plus vascular access type, presence of DM, hypertension, CVD, and other comorbidities.

Multiple imputations using chained equations with ten repetitions were used to overcome missingness in baseline covariates, preventing subjects from being excluded due to missing data. Age, sex, single-pool Kt/V, BMI, hemoglobin, and comorbid conditions were the variables in the study that had no missing values. Ferritin (n=2), albumin (n=4), phosphorus (n=5), PTH (n=23), and CRP (n=10) were among the variables that necessitated imputing. All analyses were performed with R statistical software version 4.0.5 using the JMbayes2 version 0.1.5, MICE version 3.9.0, and survminer version 0.4.7 packages. All tests were two-tailed, and P values <.05, were considered statistically significant.

## RESULTS

After excluding patients who withdrew from hemodialysis within three months of initiation (n=26), or developed cancer (n=19) or hepatic cirrhosis (n=7), we analyzed 408 patients who underwent hemodialysis. The mean (SD) age was 62.2 (12.3) years and 208 (50.7%) were male. The mean (SD) baseline BMI was 25.3 (5.3) kg/m². Of the 408 patients, 148 (36.3%) had diabetes mellitus, 286 (70.1%) had hypertension, and 137 (33.6%) had CVD. At baseline, the mean (SD) mCI was 18.02 (3.00). The baseline parameters are shown in **Table 1** according to the tertiles of mCI slopes.

### Longitudinal characteristics

The 4477 observations with a median count (IQR) of 9 (5, 15.25) were used to assess mCI changes over a median (IQR) follow-up of 2.16 (1.13, 3.73) years. Data were available for 78.2 percent of patients for up to one year, 53.9 percent for up to two years, and 32.8 percent for up to three years. Using the joint model of the longitudinal component, the change rate of the mCI varied from -0.30 to 0.23 mg/kg/day each year. Deaths occurred due to cardiovascular (n=95), cancer (n=5), infection (n=46), and unexplained reasons (n=42) throughout the follow-up period. When moving from tertile 1 (rapid decliners) to tertile 3 of the mCI slope, there was a tendency of declining values for several variables, such as age, the prevalence of hypertension, and CVD. Subjects with a greater mCI slope (constant or increasing CI over time) had a higher BMI, were more likely to have an arteriovenous fistula (AVF), and had higher baseline blood albumin concentrations (**Table 1**).

### Temporal patterns of the modified creatinine index

According to the survival state, the multivariate-adjusted mean trajectory for mCI (versus time) exhibited a consistent drop over time with a steeper slope in the presence of all-cause death (**Figure 1a**). Table 2 shows the adjusted mean slopes of creatinine, mCI, and BMI in the overall period and the slope differences between the dead and censored patients. **Figure 1b** illustrates the marginal and balanced survival curves estimated from the joint model between tertiles of random slopes, applying fully adjusted Cox regression as a separate

**Table 1.** Baseline characteristics of the study cohort according to overall and tertiles of slopes of modified creatinine index.

| | Overall | Tertile 1 (-0.3, -0.03) | Tertile 2 (-0.03, 0.04) | Tertile 3 (0.04, 0.24) | *P* value |
|---|---|---|---|---|---|
| n | 408 | 136 | 136 | 136 | |
| Age (years) | 62.17 (12.33) | 63.78 (11.90) | 63.19 (12.31) | 59.55 (12.43) | *.009* |
| Male | 207 (50.7) | 66 (48.5) | 72 (52.9) | 69 (50.7) | .767 |
| Baseline BMI (kg/m²) | 25.32 (5.25) | 24.68 (5.28) | 24.87 (5.24) | 26.42 (5.09) | **.011** |
| Dialysis vintage (years) | 4.10 (2.10, 7.43) | 4.65 (2.30, 8.27) | 3.70 (2.00, 7.30) | 4.50 (2.10, 7.40) | .398 |
| Vascular access (AVF) | 189 (46.3) | 45 (33.1) | 63 (46.3) | 81 (59.6) | **<.001** |
| Comorbidities | | | | | |
| Diabetes mellitus | 148 (36.3) | 48 (35.3) | 57 (41.9) | 43 (31.6) | .202 |
| Hypertension | 286 (70.1) | 101 (74.3) | 101 (74.3) | 84 (61.8) | **.034** |
| Cardiovascular disease | 137 (33.6) | 43 (31.6) | 57 (41.9) | 37 (27.2) | **.031** |
| Others | 42 (10.3) | 11 (8.1) | 19 (14.0) | 12 (8.8) | .220 |
| Hemoglobin (g/dL) | 11.07 (2.07) | 10.87 (1.87) | 11.17 (2.17) | 11.17 (2.16) | .395 |
| Ferritin (µg/L) | 287.30 (158.07, 485.50) | 284.45 (157.88, 444.08) | 310.05 (176.95, 541.92) | 262.00 (150.78, 467.15) | .144 |
| Phosphorus (mg/dL) | 5.04 (1.60) | 5.09 (1.66) | 5.08 (1.63) | 4.96 (1.51) | .737 |
| PTH (µg/L) | 216.50 (113.80, 408.45) | 239.10 (122.20, 488.70) | 189.70 (115.08, 391.20) | 212.40 (93.43, 382.42) | .151 |
| Serum albumin (g/dL) | 3.59 (0.22) | 3.57 (0.20) | 3.58 (0.22) | 3.63 (0.22) | **.021** |
| C-reactive protein (mg/dL) | 5.40 (2.70, 9.62) | 5.90 (2.88, 10.10) | 4.85 (2.68, 9.25) | 4.75 (2.85, 9.35) | .590 |
| Serum creatinine (mg/dL) | 7.60 (2.08) | 7.37 (1.84) | 7.58 (2.00) | 7.85 (2.35) | .163 |
| Modified creatinine index (mg/kg/day) | 18.02 (3.00) | 17.35 (3.01) | 18.31 (2.91) | 18.41 (2.97) | **.005** |
| Single-pool (Kt/V) | 1.25 (0.18) | 1.24 (0.18) | 1.24 (0.18) | 1.26 (0.19) | .764 |

Normally distributed continuous variables are presented as mean (standard deviation), and non-normally distributed variables as median (25th–75th percentile). Categorical variables are presented as numbers and percentages. BMI: body mass index, AVF: arteriovenous fistula. The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Table 2.** Linear mixed-effects regression results of longitudinal responses modelled separately, according to overall time and outcome (death or censored) status with time interaction.

| | Exposure variables | | | | | |
|---|---|---|---|---|---|---|
| Longitudinal response variables | Time | | | Status-time interaction[a] | | |
| | Estimates | 95% CI | *P* value | Estimates | 95% CI | *P* value |
| Serum creatinine (mg/dL) | -0.20 | -0.52, 0.13 | .241 | -0.36 | -0.39 -0.32 | <.001 |
| Modified creatinine index (mg/kg/day) | -0.22 | -0.41, -0.04 | .019 | -0.31 | -0.33, -0.29 | <.001 |
| Body mass index (kg/m²) | 0.07 | -0.10, 0.24 | .414 | -0.39 | -0.41, -0.38 | <.001 |

Models were adjusted with age, sex, phosphorus, parathyroid hormone, hemoglobin, ferritin, dialysis vintage, and single-pool Kt/V, vascular access type, presence of diabetes mellitus, hypertension, cardiovascular disease, and other comorbidities. [a]Death vs censored. CI, confidence interval.

model. The consequences of univariate and multivariate joint models with hazard ratios (HRs) for the relationship between all-cause mortality and two patterns of mCI (level and slope), adjusted for baseline covariates in the univariate joint model and additionally adjusted for BMI trajectories over time in the multivariate joint model are shown in **Table 3**.

A yearly 1 mg/kg/day reduction in mCI level was associated with an increased risk of all-cause death (HR, 1.04; 95% CI, 1.02-1.07; *P*=.001), according to a crude univariate model in which the longitudinal submodel was adjusted for a sampling period, and the survival submodel was adjusted for baseline m - mCI levels. Although the impact of the mCI trend on survival decreased, statistical significance remained after adjusting for baseline clinical features and laboratory indicators. After controlling for BMI trajectories in the multivariate model, the association remained unchanged (**Table 3**). An annual 0.1 unit rise in the rate of decline in mCI was related to an increased risk of all-cause death (HR, 1.23; 95% CI, 1.15-1.33; *P*=.001), according to a raw univariate model for the rate of change in mCI. In a fully adjusted model, the hazard ratio was 1.04 (95% CI, 1.01-1.06; *P*=.017). After controlling for BMI trajectories and baseline factors in a multivariate model, the association between the rate of decline in mCI and the endpoint was not substantially changed (**Table 3**).

## DISCUSSION

The association between the trajectory of the mCI, which is a surrogate marker of LBM, and mortality was assessed in hemodialysis patients in this study. The results indicated that a reduction in mCI level with time was associated with a poor prognosis in this population. In the multivariate regression, controlling for other factors had no significant impact on the association, demonstrating that the link was not dependent on these potentially confounding effects. Furthermore, after the confounding effect of BMI trajectory was corrected using the multivariable model, the mCI trajectory still affected survival. We can thus conclude from the results that repetitive mCI levels may be a valuable tool for identifying hemodialysis patients at risk of death. These data also emphasize the need for monitoring this group's health, which may allow physicians to better focus preventative treatments and minimize the likelihood of unfavorable outcomes.

The findings in our research are consistent with those of several previous studies, at least in terms of initial values. The creatinine index has been reported to be an accurate tool for longitudinal observation of

nutritional condition in patients undergoing maintenance hemodialysis.[20,21] Yamada et al reported that a lower creatinine index was associated with all-cause mortality in maintenance hemodialysis patients. They also determined that mCI values tested at two separate times correlated, suggesting that the index seems to be a robust indicator of muscle mass that is unaffected by hydration state.[22,23] According to Suzuki et al, the
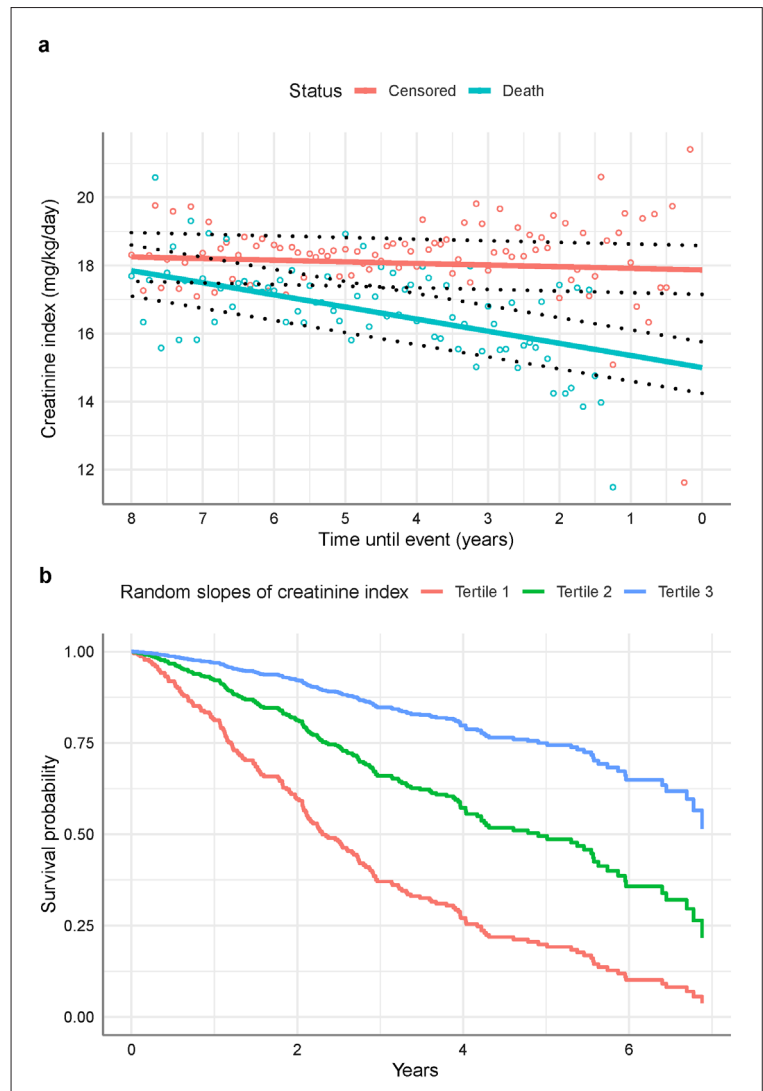


**Figure 1.** Upper panel (a) shows fitted mean longitudinal trajectory of modified creatinine index (solid colorful lines) for patients who were censored or reached an endpoint, as predicted by fully adjusted linear mixed modeling regression analysis (with baseline creatinine index as part of the dependent variable). Circular shapes denote mean creatinine index levels in varying time points. In censored patients, creatinine index levels show relatively a slight decreasing tendency over time. By contrast, patients who experienced an event, creatinine index levels show a steeper decline. Dashed lines depict 95% CI. Lower panel (b) displays marginal and balanced survival curves according to tertiles of slopes of creatinine index, which were estimated using a fully adjusted Cox proportional hazard model.

**Table 3.** Associations between modified creatinine index trajectories as a surrogate marker of lean body mass and all-cause mortality.

| | Univariable joint model | | Multivariable joint model[a] | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| **Level** | | | | |
| Crude model | 1.859 (1.640, 2.106) | <.001 | 1.598 (1.443, 1.766) | <.001 |
| Model 1 | 1.047 (1.023, 1.073) | <.001 | 1.047 (1.018, 1.073) | <.001 |
| Model 2 | 1.047 (1.018, 1.073) | .001 | 1.042 (1.018, 1.062) | .002 |
| Model 3 | 1.042 (1.018, 1.068) | <.001 | 1.042 (1.018, 1.068) | <.001 |
| Model 4 | 1.042 (1.018, 1.068) | <.001 | 1.042 (1.013, 1.068) | .001 |
| **Slope** | | | | |
| Crude model | 1.231 (1.146, 1.328) | <.001 | 1.182 (1.084, 1.286) | <.001 |
| Model 1 | 1.114 (1.068, 1.168) | <.001 | 1.102 (1.052, 1.175) | <.001 |
| Model 2 | 1.079 (1.042, 1.127) | <.001 | 1.068 (1.027, 1.108) | <.001 |
| Model 3 | 1.057 (1.023, 1.090) | .007 | 1.057 (1.018, 1.084) | <.001 |
| Model 4 | 1.037 (1.009, 1.062) | .017 | 1.042 (1.009, 1.073) | .011 |

Hazard ratios (HRs) and 95% CIs are presented per one-unit annual decrease in creatinine index for level parametrization, and per 0.1-unit annual increase in the rate of decrease in creatinine index for slope parametrization, estimated by joint longitudinal-survival model. The model links linear mixed effect (LME) models for the trajectories of the biomarker with Cox proportional hazard models for the time-to-event data. Crude model: Cox model unadjusted, LME model adjusted for sampling time; Model 1: Cox and LME models adjusted for age, sex, phosphorus, and PTH; Model 2: Cox and LME models adjusted for Model 1 plus hemoglobin, ferritin, dialysis vintage, and single-pool Kt/V; Model 3: Cox and LME models adjusted for Model 2 plus baseline body mass index (BMI), albumin, and C-reactive protein (CRP); Model 4: Cox and LME models adjusted for Model 3 plus vascular access type, presence of diabetes mellitus, hypertension, cardiovascular disease, and other comorbidities.

[a]Multivariable joint model additionally adjusted for BMI trajectories.

difference in the mCI between two measurements over a year enhanced the prediction of mortality in dialysis patients, suggesting that the mCI is also worthy as a time-dependent marker for assessing muscle mass.[10] Reduced skeletal muscle mass, as measured by a lower modified creatinine index, was linked to an increased risk of cardiac disease and all-cause death in patients on HD, according to Arase et al.[9] Yamamoto et al found that the mCI was linked to long-term consequences after controlling for handgrip strength and gait speed, indicating that the mCI can be used to diagnose sarcopenia in dialysis patients.[24] A time-to-event study based on the measurement of a single biomarker is essential for assessing individual risk. However, it may offer inadequate data regarding the clinical history of a disease. We assumed that repeated mCI values and their temporal changes (slopes) may be associated with all-cause mortality and may have additional benefits for patient surveillance and prognosis estimation. We used the joint modeling approach to assess the relationship between a longitudinal biomarker trajectory and a time-to-event endpoint like death.[25] Unlike previous studies, our study emphasizes the importance of measuring mCI levels throughout time. This problem

is addressed by the joint modeling technique, which assumes that the results are computed with an error. In particular, correcting for baseline values to decrease regression to the mean has also been suggested, and the random intercept in the longitudinal submodel can help with this.[26]

Several factors may lead to sarcopenia in dialysis patients, such as inadequate nutrition, inflammation, and hormonal disorders.[27] Especially, inflammation could be an essential mediator in accelerating the degradation of muscle proteins. Furthermore, myokines produced by skeletal muscle would reduce inflammation and insulin resistance, thereby suppressing the pro-inflammatory effects of illness; therefore, the relative absence of myokines in sarcopenic individuals may increase the risk of cardiovascular disease and mortality.[28,29] On the other hand, it does not seem possible to conclude that sarcopenia alone causes death. With the combination of many factors that lead to sarcopenia, we could infer that this is a pathological consequence. Muscle loss might, therefore, be considered a harbinger of impending death.

Our research's strength and originality are that it focuses on the yearly rate of mCI reduction. To de-

termine this quantitative result, the joint longitudinal survival model incorporates information on temporal variations in biomarkers and observed time to event at the same time. Compared to other invasive and costly approaches, measuring mCI is relatively simple. However, our observations must be evaluated in light of the shortcomings of the study. First, residual confounding or any other unmeasured inflammation-related variables might have biased the results. Second, protein intake and dialysis dose may affect serum creatinine concentrations, while serum creatinine primarily stems from muscle mass. However, when calculating mCI, Kt/V is included in the formula. Furthermore, according to a recent study, mCI values between time points had a strong correlation.[22] Third, residual kidney function did not exist in our data, which may have affected the mCI levels. Because residual glomerular filtration rate strongly predicts survival,[31] it may modify the link between mCI and mortality. Even though our database had no information on residual glomerular filtration rate, creatinine has been suggested to be an excellent muscle mass marker in hemodialysis patients.[30] Furthermore, the mCI was shown to be highly correlated to muscle mass, as measured by BIA or upper arm diameter, despite correcting for the estimated glomerular filtration rate.[10] Fourth, the study has the inherent limitations of a retrospective study. Data were obtained from medical records that were not explicitly considered to address the association between the mCI trajectory and prognosis. Finally, since the sample consisted of people from a particular geographical location, the findings may not be generalizable to other groups.

In conclusion, patients with decreased LBM over time, as estimated by the mCI, had a higher mortality risk than those with stable or a slowly decreasing LBM over time. In addition, after correcting for BMI trajectory, the relationship remained significant. The mCI is a simple and quick test for clinical use that does not require special equipment. The mCI trajectory could also be a potential biomarker for stratifying patients at risk of undergoing hemodialysis therapy.

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