Original Article

Association of nutritional status with osteoporosis, sarcopenia, and cognitive impairment in patients on hemodialysis

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Background and Objectives: Inadequate nutrition in patients on hemodialysis causes various complications. This study aimed to investigate the association between nutritional status and risk of osteoporosis, sarcopenia, and cognitive impairment in patients on hemodialysis. **Methods and Study Design:** We enrolled 131 older patients on maintenance hemodialysis. Geriatric Nutrition Risk Index (GNRI) was used to assess nutritional status. Patients were divided into quartile groups according to the GNRI. Dual-energy X-ray absorptiometry, bioimpedance analysis and handgrip strength measurement, and the Korean version of the Montreal Cognitive Assessment were used to assess osteoporosis, sarcopenia, and cognitive impairment, respectively. Biochemical laboratory tests were also performed before mid-week hemodialysis session. **Results:** Patients from higher GNRI quartiles had a lower prevalence of osteoporosis and sarcopenia. Cognitive impairment was not associated with any GNRI quartile. In the multivariable models, longer dialysis periods (OR 1.696, 95% CI 1.053-2.729, p=0.030) and higher intact parathyroid hormone levels (OR 3.136, 95% CI 1.781-5.518, p<0.001) were significantly associated with osteoporosis risk. GNRI quartile 2 (OR 0.064, 95% CI 0.005-0.883, compared to quartile 1, p=0.040) and higher hemoglobin A1c levels (OR 3.728, 95% CI 1.033-86.4, p=0.043) were associated with a higher sarcopenia risk. Lower hemoglobin levels (OR 0.585, 95% CI 0.360-0.950, p=0.030) were associated with a higher risk of cognitive impairment. **Conclusions:** In patients on hemodialysis, inadequate nutrition was associated with the risk of osteoporosis and sarcopenia, but not cognitive impairment. Proper nutritional assessment and management in these patients could prevent complications related to bone and muscle loss.

Key Words: malnutrition, sarcopenia, osteoporosis, hemodialysis, cognitive impairment

INTRODUCTION

The importance of assessing and managing malnutrition has attracted much attention recently. In patients with end-stage kidney disease (ESKD), musculoskeletal weakness and osteoporosis frequently occurs related to poor nutritional status.[1] Particularly, osteoporosis is accelerated by chronic kidney disease-mineral bone disorder (CKD-MBD).[2] Osteoporosis is characterized by low bone mass, microarchitectural disruption, and skeletal fragility, all of which result in decreased bone strength and increased risk of fracture.[3] Indeed, the fracture incidence is significantly higher in patients on dialysis than in predialysis patients, resulting in increased mortality and reduced quality of life (QOL).[4,5]

Moreover, malnutrition causes protein-energy wasting (PEW), which is the state of decreased body protein and energy stores associated with nutritional metabolic derangement.[6] Persistent PEW could lead to sarcopenia.[7] Sarcopenia is characterized by muscle mass loss and limited exercise capacity and muscle function.[8] Hemodialysis patients experience faster muscle loss and a decline in physical capacity than healthy people.[7] These factors negatively affect daily life and are associated with a higher risk of falls.[9] In ESKD patients, the frequency of sarcopenia is even greater because uremia-induced anorexia, acidosis, anemia, and hormonal derangements inhibit

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muscle synthesis and accelerate muscle wasting.[10] Moreover, decreased muscle strength was found to be an independent predictor of survival in hemodialysis patients.[11] Bones and muscles are not only adjacent but also chemically and metabolically related. Therefore, osteoporosis and sarcopenia have common risk factors and biological pathways and are both associated with significant physical disability.[12] The coexistence of these two diseases is associated with a high risk of falls and fractures, hospitalization, and poorer QOL.[12]

The incidence of sarcopenia resulting from malnutrition increases with age and is associated with physical inactivity and higher body fat percentages.[13] These modifiable risk factors are, in turn, associated with pathological processes leading to cognitive impairment.[14] Cognitive impairment increases the risk of functional decline in older hemodialysis patients.[15] Furthermore, cognitive impairment is an independent predictor of all-cause mortality in maintenance hemodialysis patients.[16]

The effects of the nutritional status of hemodialysis patients on osteoporosis, sarcopenia, and cognitive impairment vary in different studies.[1,2,9,12,17-19] To date, various nutrition assessment tools have been developed, including mini nutritional assessment short form, nutrition risk score, malnutrition screening tool, and geriatric nutritional risk index (GNRI).[20] Of these diverse tools, GNRI is preferable as it could be easily calculated from serum albumin, sex, height, and body weight and has been validated as an accurate nutrition assessment tool in previous studies.[20,21] GNRI has also been reported to predict all-cause and cardiovascular mortality in ESKD patients.[22] Therefore, we used GNRI to assess nutritional status in hemodialysis patients. This study aimed to explore the association between nutritional status and risks of osteoporosis, sarcopenia, and cognitive impairment in hemodialysis patients.

METHODS

Study subjects

We recruited maintenance hemodialysis patients from Maryknoll Medical center in Korea between September and December 2018. Inclusion criteria were as follows: (1) receiving hemodialysis three times a week, (2) maintaining hemodialysis for at least 3 months, (3) willingness to participate in the study. Patients aged <50 years and those having infections and hemorrhages within 3 months of the study period, malignant tumors, or chronic inflammatory diseases were excluded, as were patients who did not undergo assessment for osteoporosis, sarcopenia, or cognitive impairment due to visual and/or hearing problem or patient refusal. Demographic data were obtained from patient interviews and confirmed via medical records. This study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Maryknoll Medical Center (IRB number: MMC/2019-293).

Nutritional status and inflammation

To assess nutritional status, we performed biochemical analyses (serum albumin, HDL cholesterol, LDL cholesterol, triglycerides, ferritin, β2-microglobulin, hemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hs-CRP), and intact parathyroid hormone (PTH]) and anthropometric measurements (body mass index (BMI) and upper-arm circumference). Blood samples for biochemical tests were collected immediately before a mid-week hemodialysis session. BMI was calculated using the equation BMI = weight / height^2 (kg/m^2), and upper-arm circumference was obtained by bioimpedance analysis (BIA) immediately after a hemodialysis session. BIA was performed using an S10 water body analyzer (InBody, Seoul, Korea). Levels of hs-CRP were measured by a latex-enhanced immunonephelometric method using a BN II analyzer (Dade Behring, Newark, DE, USA). GNRI was also calculated according to the baseline serum albumin level, body weight, and ideal body weight to assess nutritional status.[23] The ideal body weight was calculated from the Lorentz equations (WLo), as follows:

For men: height – 100 – [(height – 150) / 4]

For women: height – 100 – [(height – 150) / 2.5]

GNRI was calculated as follows:

GNRI = [14.89 × albumin (g/dL)] + [41.7 × (weight / WLo)].

Using the calculated GNRI, we divided participants into GNRI quartile groups and evaluated the associations of GNRI quartiles with osteoporosis, sarcopenia, and cognitive impairment.

Bone mineral density and osteoporosis

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) using a Discovery Wi fan-beam densitometer (Hologic Inc., Bedford, MA, USA). T-scores of left total femur, left femur neck, and lumbar spine (L1-L5) bone densities were used. All scans and calculations were performed by one radiologic technologist to minimize variations in measurements. The T-score was used to represent the absolute risk of fracture relative to the bone density of the youngest age group with the highest bone mass. According to the guidelines of the World Health Organization, patients with a T-score below -2.5 standard deviations were classified as having osteoporosis, while those with a T-score of -1.0 to -2.5 standard deviations were classified as having osteopenia.

Parameters for sarcopenia

We measured muscle mass and strength of all the participants to diagnose sarcopenia. Appendicular muscle mass index (ASM/h^2), a widely used and well-validated parameter, was used to evaluate muscle mass.[24] ASM/h^2 was calculated by dividing the sum of the limb muscle mass by the square of the height. If this value was <2 standard deviations in the younger population, it was defined as a low muscle mass index (<7.0 kg/m^2 in men and <5.4 kg/m^2 in women).[24] BIA, which has been recommended as a good alternative to DXA by the European Working Group on Sarcopenia in Older People,[25] was used to measure quantitative muscle mass. BIA has been validated in various populations including old adults, Asians, Koreans, and hemodialysis patients.[26-29] Compared to DXA, BIA is easily applicable in clinical practice and relatively cheap and does not pose a radiation hazard. To determine muscle strength, we measured handgrip strength (HGS) using a digital grip strength dynamometer (T.K.K. 5401; Takei Scientific In-

struments Co., Ltd., Tokyo, Japan). HGS was measured after a dialysis session using the non-fistula arm of the subject and with the subject standing with both arms extended sideways from the body with the dynamometer facing away from the body. Three trials were performed with a rest period of at least 1 min between trials, and the average values were recorded.[30] Low muscle strength was classified as an HGS value of <26 and <18 kg in men and women, respectively. In this study, we adopted the Asian Working Group for Sarcopenia (AWGS) criteria.[24] Presarcopenia was defined as having low muscle mass and normal muscle strength, and sarcopenia as having low muscle mass and low muscle strength.

Cognitive function

Several studies have reported that the Montreal Cognitive Assessment (MoCA) can assess all cognitive domains and is sensitive to cognitive abnormalities in patients with mild cognitive impairment or dementia.[31,32] In our study, the Korean version of the Montreal Cognitive Assessment (K-MoCA) was used to evaluate cognitive status. The MoCA includes items to assess visuospatial and executive function (5 points), naming (3 points), memory (5 points), attention (6 points), abstraction (2 points), language (3 points), and orientation (6 points). The difference between the K-MoCA and the MoCA is that the K-MoCA presents the naming part as lion, bat, and rhinoceros instead of lion, rhinoceros, and camel. Data were obtained via interviews with the patients. The K-MoCA scores range from 0 to 30, and higher scores indicate better cognitive status. The most widely accepted and frequently used cutoff score for the K-MoCA is 23, with scores of ≤23 indicating mild cognitive impairment.[33]

Statistical analysis

All analyses were performed using IBM SPSS (Version 25.0, IBM, NY, USA). Data are presented as the mean ± standard deviation for continuous variables and as proportions for categorical variables. The continuous variables were compared with one-way analysis of variance or Kruskal-Wallis test according to the result of the normality test. For categorical variables, Pearson's chi-squared test was performed if the expected frequency was ≥5; otherwise, Fisher's exact test was performed. The GNRI quartile was analyzed as a categorical variable with quartile 1 as a reference. Osteoporosis status was treated as categorical variable with three categories (normal, osteopenia, and osteoporosis). Sarcopenia status and cognitive impairment were treated as binary categorical variables (normal and abnormal). Univariate and multivariate logistic regression analyses were applied to evaluate the association between nutritional status and osteoporosis status, sarcopenia status, and cognitive impairment. For osteoporosis status, ordinal logistic regression analysis was performed and the parallel regression assumption was checked for the model coefficients. Variables in multivariate models were selected using stepwise backward selection. p values <0.05 were considered statistically significant.

RESULTS

Correlations of GNRI with osteoporosis, sarcopenia, and cognitive impairment

This study included 131 hemodialysis patients whose mean age was 66.2±10.5 years. Among them, 54.2% (n=71) were men and 67.9% (n=89) had diabetes. Table 1 compares the patient characteristics by GNRI quartile. The quartile cutoffs were ≤96, 97-101, 102-107, and ≥108 from quartile 1. The mean quartile GNRI values were 91.7±4.6, 99.2±1.5, 104.8±1.6, and 114.0±4.9 from quartile 1 to quartile 4, respectively. Higher GNRI quartiles indicated a better nutritional status. Compared with GNRI quartile 1, quartile 4 was associated with higher femur T-scores and lumbar spine T-scores as well as higher triglyceride, HbA1c, albumin, BMI, upper-arm circumference, and skeletal muscle mass index values. Higher GNRI quartiles were also associated with a lower prevalence of osteoporosis and sarcopenia. However, there were no differences in sex, cause of ESKD, prevalence of diabetes, age, hemodialysis duration, HGS, and cognitive status among the quartiles. There were also no differences in hemoglobin, LDL cholesterol, HDL cholesterol, β2-microglobulin, or ferritin levels. As shown in Figure 1, higher quartiles of GNRI showed less frequent osteoporosis and sarcopenia (p value for trends=0.001 and 0.002, respectively). However, no significant association was found between cognitive impairment and GNRI quartiles (p value for trends=0.40).

Determinants of osteoporosis

Table 2 shows the baseline characteristics of participants with osteopenia or osteoporosis. The percentages of patients with normal bone, osteopenia, and osteoporosis were 16.8% (n=22), 44.3% (n=58), and 38.9% (n=51), respectively. Compared with the normal bone group, the osteopenia and osteoporosis groups had more female and older patients. LDL cholesterol, HDL cholesterol, and intact PTH levels were higher in osteopenia and osteoporosis patients. On the other hand, GNRI quartile, HGS, BMI, upper-arm circumference, skeletal muscle mass index, and MoCA total score were lower in osteopenia and osteoporosis patients. Of the GNRI quartile groups, quartile 4 showed a significant difference in osteoporosis status (p value=0.002). Table 3 lists variables related to osteopenia and osteoporosis incidence based on a univariate and multivariate logistic regression analysis considering subjects with normal bone, osteopenia, and osteoporosis. In the univariate model, female sex, age, duration of dialysis, and LDL cholesterol, HDL cholesterol, and intact PTH levels were positively correlated with osteopenia and osteoporosis. Meanwhile, GNRI quartile 4, HGS, BMI, upper-arm circumference, skeletal muscle mass index, and MoCA total score showed a significant negative correlation with osteopenia and osteoporosis. Multivariate logistic regression analysis was adjusted for confounders, including age, sex, body mass index, and diabetes. The longer the duration of dialysis (OR 1.696, 95% CI 1.053-2.729) and the higher the intact PTH level (OR 3.136, 95% CI 1.781-5.518), the more frequent osteoporosis occurred.

Table 1. Comparison of baseline characteristics among chronic hemodialysis patients stratified by GNRI quartile

Variables	GNRI quartile 1 (N=33)	GNRI quartile 2 (N=35)	GNRI quartile 3 (N=33)	GNRI quartile 4 (N=30)	*p*-value
Sex, male, n (%)	21 (63.6)	16 (45.7)	17 (51.5)	17 (56.7)	0.508
Cause of ESKD, n (%)					0.723
Diabetic	17 (51.5)	25 (71.4)	22 (66.7)	22 (73.3)	
Hypertensive	2 (6.1)	0 (0)	0 (0)	1 (3.3)	
Glomerulonephritis	2 (6.1)	2 (5.7)	3 (9.1)	2 (6.7)	
PCKD	2 (6.1)	2 (5.7)	1 (3)	0 (0)	
Other	2 (6.1)	2 (5.7)	0 (0)	1 (3.3)	
Unknown	8 (24.2)	4 (11.4)	7 (21.2)	4 (13.3)	
Diabetes, n (%)	18 (54.5)	26 (74.3)	23 (69.7)	22 (73.3)	0.282
Age (years)	67.8±10.7	67.6±9.64	65.7±11.1	63.4±10.7	0.329
Dialysis duration (months)	54.9±48.1	65.4±41.5	67.4±50.2	56.6±40.3	0.366
Femoral neck T-score	-2.22±0.98	-2.11±1.21	-2.03±0.92	-1.27±1.45	0.005†,¶
Lumbar spine T-score	-1.26±1.66	-1.45±1.56	-1.01±1.21	-0.22±1.6	0.009†,¶
Hemoglobin (g/dL)	10.9±0.8	11.0±1.2	11.2±1.0	10.9±0.9	0.345
LDL-cholesterol (mg/dL)	84.0±33.5	79.5±23.8	81.3±26.7	78.6±30.1	0.868
Triglyceride (mg/dL)	91±49	103±54	127±65	166±197	0.031†
HDL-cholesterol (mg/dL)	53.3±17.2	50.7±18.5	48.0±16.6	44.8±14.1	0.107
ß2-microglobulin (mg/L)	19.8±6.4	20.6±5.3	18.7±5.9	19.2±5.0	0.816
Serum ferritin (μg/L)	351±336	348±260	340±243	352±236	0.917
HbA1c	5.8±0.93	6.29±1.17	6.59±1.26	6.59±1.09	0.012†, ‡
Hs-CRP	6.79±11.81	1.78±2.91	3.83±6.46	2.64±4.34	0.191
Intact PTH (pg/mL)	203±137	215±211	167±115	194±112	0.709
Albumin (g/dL)	3.61±0.33	3.87±0.24	4.03±0.25	4.21±0.28	<0.001†, ‡, §,¶
Handgrip strength (kg)	20.3±8.1	18.3±5.7	20.1±7.3	23.7±9.0	0.099
Body mass index (kg/m^2)	20.3±1.8	22.1±1.8	23.9±2.3	27.4±2.7	<0.001†, ‡, §,¶,††,‡‡
Upper arm circumference (cm)	23.5±2.7	23.7±2.1	23.7±4.2	26.8±3.7	<0.001†,¶, ‡‡
Appendicular muscle mass index (kg/m^2)	7.14±1.43	7.18±1.11	7.3±1.05	8.35±1.33	<0.001†,¶, ‡‡
MoCA total score	23.2±3.9	22.5±4.3	22.2±4.7	21.9±5.1	0.897
Visuospatial executive	4.06±1.06	3.49±1.36	3.79±1.32	3.43±1.55	0.284
Naming	2.91±0.29	2.86±0.43	2.64±0.78	2.87±0.35	0.282
Attention	5.27±1.18	4.94±1.06	4.91±1.23	4.87±1.61	0.328
Language	2.45±0.56	2.29±0.75	2.3±0.77	2.33±0.84	0.881
Abstraction	1.79±0.48	1.69±0.58	1.7±0.64	1.53±0.73	0.489
Delayed recall	1.09±1.35	1.6±1.5	1.36±1.48	1.57±1.59	0.472
Orientation	5.61±0.79	5.63±0.6	5.52±0.62	5.33±0.84	0.298
Osteoporosis status, n (%)					0.007
Normal	3 (9.1)	5 (14.3)	3 (9.1)	11 (36.7)	0.018
Osteopenia	14 (42.4)	11 (31.4)	20 (60.6)	13 (43.3)	0.113
Osteoporosis	16 (48.5)	19 (54.3)	10 (30.3)	6 (20)	0.016
Sarcopenia status, n (%)					0.018
Normal	24 (72.7)	31 (88.6)	29 (87.9)	30 (100)	0.010
Presarcopenia	1 (3)	2 (5.7)	1 (3)	0 (0)	0.902
Sarcopenia	8 (24.2)	2 (5.7)	3 (9.1)	0 (0)	0.009
Cognitive impairment, n (%)	11 (33.3)	14 (40)	15 (45.5)	14 (46.7)	0.687

GNRI: geriatric nutrition risk index; ESKD: end-stage kidney disease; PCKD: polycystic kidney disease; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; intact PTH: intact parathyroid hormone; MoCA total score: Montreal cognitive assessment total score.
All data are expressed as means±SD. Adjusted *p*-value was obtained using Bonferroni correction for three groups.
† Adjusted $p< 0.05$ GNRI 4 vs. GNRI 1. ‡ Adjusted $p<0.05$ GNRI 3 vs. GNRI 1. § Adjusted $p<0.05$ GNRI 2 vs. GNRI 1. ¶ Adjusted $p<0.05$ GNRI 4 vs. GNRI 2. †† Adjusted $p<0.05$ GNRI 3 vs. GNRI 2. ‡‡ Adjusted $p<0.05$ GNRI 4 vs. GNRI 3.

Determinants of sarcopenia

Among 131 patients, 4 (3.1%) and 13 (9.9%) patients were diagnosed with presarcopenia and sarcopenia, respectively. In Table 4, we compare normal, presarcopenia, and sarcopenia according to the AWGS criteria to identify variables associated with sarcopenia development. The GNRI quartile, femoral neck T-score, lumbar spine T-score, BMI, upper-arm circumference, and skeletal muscle mass index were low in patients with sarcopenia. Furthermore, the percentage of patients with diabetes and the rate of ESKD due to diabetes were high in the normal group. Table 5 shows the variables associated with the development of sarcopenia by univariate and multivariate logistic regression. In the univariate model, sarcopenia is associated with diabetes, lower femoral neck and lumbar spine T-scores, higher HDL levels, lower BMI, and shorter upper-arm circumference. Multivariate logistic regression analysis was adjusted for sex, diabetes, age, and BMI. Patients from GNRI quartile 2, relative to quartile 1, showed a lower frequency of sarcopenia (OR 0.064, 95% CI 0.005-0.883). Moreover, the higher the HBA1c level, the higher the incidence of sarcopenia (OR 2.960, 95%CI 1.033-8.486).

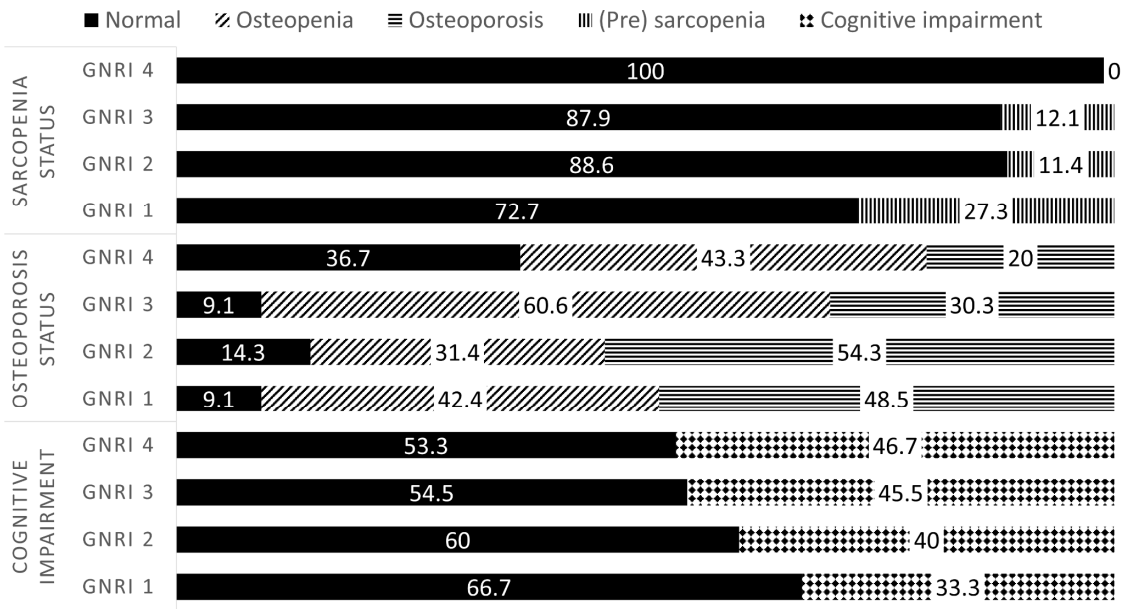

Figure 1. Distributions of sarcopenia status (normal and presarcopenia), osteoporosis status (normal, osteopenia, and osteoporosis), and cognitive impairment (normal function and cognitive impairment) are plotted by Geriatric Nutrition Risk Index (GNRI) quartile. The lower the GNRI quartile, the higher the incidence of osteopenia and osteoporosis (p=0.007). The incidence of presarcopenia also increased as the GNRI quartile decreased (p=0.018). In the case of cognitive impairment, the frequency of occurrence increased with increasing GNRI quartile. However, no statistical difference was found (p=0.687).

Table 2. Baseline characteristics of participants with osteopenia or osteoporosis

Variables	Normal (N=22, 16.8%)	Osteopenia (N=58, 44.3%)	Osteoporosis (N=51, 38.9%)	p-value
Sex, male, n (%)	18 (81.8)	43 (74.1)	10 (19.6)	<0.001#,†
Cause of ESKD, n (%)				0.113
Diabetic	15 (68.2)	40 (69)	31 (60.8)	
Hypertensive	0 (0)	3 (5.2)	0 (0)	
Glomerulonephritis	3 (13.6)	2 (3.4)	4 (7.8)	
PCKD	1 (4.5)	1 (1.7)	3 (5.9)	
Other	0 (0)	0 (0)	5 (9.8)	
Unknown	3 (13.6)	12 (20.7)	8 (15.7)	
Diabetes, n (%)	15 (68.2)	43 (74.1)	31 (60.8)	0.329
GNRI stage, n (%)				0.004
Q1	3 (13.6)	14 (24.1)	16 (31.4)	0.269
Q2	5 (22.7)	11 (19)	19 (37.3)	0.088
Q3	3 (13.6)	20 (34.5)	10 (19.6)	0.080
Q4	11 (50)	13 (22.4)	6 (11.8)	0.002†
Age (years)	60.6±11.3	66.2±11.2	68.6±8.5	0.031†
Dialysis duration (months)	47.9±32.5	57.4±33.6	71.4±57.9	0.320
Hemoglobin (g/dL)	11.0±1.0	11.1±0.9	10.9±1.1	0.880
LDL-cholesterol (mg/dL)	82.4±27.7	71.8±23.8	90.6±30.6	0.005†
Triglyceride (mg/dL)	126±118	128±138	109±55.5	0.903
HDL-cholesterol (mg/dL)	43.6±15.0	46.5±15.1	55.0±18.1	0.004†, §
ß2-microglobulin (mg/L)	19.6±4.8	19.5±6.0	19.7±5.7	0.947
Serum ferritin (μg/L)	358±176	329±238	365±332	0.490
HbA1c	6.3±1.08	6.44±1.18	6.17±1.16	0.464
Hs-CRP	5.71±11.62	3.25±5.92	3.48±6.59	0.340
Intact PTH (pg/mL)	145±88	172±121	246±186	0.038†, §
Albumin (g/dL)	4.02±0.35	3.94±0.32	3.86±0.38	0.348
Handgrip strength (kg)	25.3±8.2	22.4±7.2	16.3±5.8	<0.001†, §
Body mass index (kg/m^2)	25±3.57	23.6±3.4	22.3±2.9	0.005†
Upper arm circumference (cm)	26.1±2.4	24.8±4.4	23.1±2.0	<0.001†, §
Appendicular muscle mass index (kg/m^2)	8.52±1.42	7.79±1.06	6.65±1.03	<0.001†, ‡, §
MoCA total score	24.4±4.3	22.7±4.4	21.4±4.4	0.009†

GNRI: geriatric nutrition risk index; ESKD: end-stage kidney disease; PCKD: polycystic kidney disease; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; intact PTH: intact parathyroid hormone; MoCA total score: Montreal cognitive assessment total score.
All data are expressed as means±SD. Adjusted p-value was obtained using Bonferroni correction for three groups
† Adjusted p<0.05 osteoporosis vs. normal. ‡ Adjusted p<0.05 osteopenia vs. normal. § Adjusted p<0.05 osteoporosis vs. osteopenia.

Table 3. Factors associated with osteopenia or osteoporosis in unadjusted and adjusted logistic models

Variables	Unadjusted model		Adjusted model†	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex, male	0.096* (0.044, 0.210)	<0.001	0.060 (0.022, 0.163)	<0.001
Diabetes	0.676 (0.337, 1.356)	0.270	1.707 (0.703, 4.154)	0.238
GNRI				
Q1	Reference			
Q2	1.107 (0.442, 2.769)	0.828	-	-
Q3	0.578 (0.230, 1.454)	0.244	-	-
Q4	0.213 (0.080, 0.566)	0.002	-	-
Age (years)	1.573* (1.126, 2.197)	0.024	1.826 (1.185, 2.812)	0.006
Dialysis duration (months)	1.503* (1.056, 2.138)	<0.001	1.696* (1.053, 2.727)	0.030
Hemoglobin (g/dL)	0.899 (0.650, 1.245)	0.523	-	-
LDL-cholesterol (mg/dL)	1.494* (1.063, 2.098)	0.021	1.220 (0.795, 1.872)	0.362
Triglyceride (mg/dL)	0.887 (0.642, 1.225)	0.466	-	-
HDL-cholesterol (mg/dL)	1.761* (1.223, 2.536)	0.002	-	-
ß2-microglobulin (mg/L)	1.024 (0.741, 1.414)	0.888	-	-
Serum ferritin (μg/L)	1.061 (0.767, 1.467)	0.723	-	-
HbA1c	0.878 (0.635, 1.214)	0.432	-	-
Hs-CRP	0.853 (0.617, 1.178)	0.335	-	-
Intact PTH (pg/mL)	1.755* (1.203, 2.560)	0.004	3.136* (1.781, 5.518)	<0.001
Albumin (g/dL)	0.733 (0.525, 1.024)	0.068	-	-
Handgrip strength (kg)	0.377* (0.255, 0.556)	<0.001	-	-
Body mass index (kg/m^2)	0.576* (0.410, 0.810)	0.002	0.347 (0.218, 0.553)	<0.001
Upper arm circumference (cm)	0.499* (0.320, 0.777)	0.002	-	-
Appendicular muscle mass index (kg/m^2)	0.275* (0.178, 0.423)	<0.001	-	-
MoCA total score	0.624* (0.444, 0.877)	0.007	0.705 (0.447, 1.111)	0.132

GNRI: geriatric nutrition risk index; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; intact PTH: intact parathyroid hormone; MoCA total score: Montreal cognitive assessment total score.

†Model was adjusted for age: sex: body mass index: and diabetes.

*p<0.05.

Determinants of cognitive impairment

Table 6 compares normal patients without cognitive impairment (58.8%, n=77) with those with cognitive impairment (41.2%, n=54). Cognitive impairment was more common in females and older people. Patients with cognitive impairment had low femoral neck T-score, HGS, and skeletal muscle mass index; however, BMI was higher in these patients. Table 7 shows the variables associated with cognitive impairment by logistic regression. In the univariate model, cognitive impairment was positively correlated with the female sex, old age, and BMI but negatively correlated with femoral neck T-score, HGS, and skeletal muscle mass index. In the multivariate logistic regression adjusted for confounders (age, sex, body mass index, and diabetes), lower hemoglobin levels were associated with a higher incidence of cognitive impairment (OR 0.585, CI 0.360-0.950). A forest plot of variables affecting osteoporosis, sarcopenia, and cognitive status after multiple logistic regression is shown in Figure 2.

DISCUSSION

Hemodialysis patients are older and susceptible to malnutrition.[34] The clinical, social, and economic problems that occur with age cause malnutrition, decreased muscle mass, and increased redistribution of total body fat.[35] PEW occurs due to increased catabolism caused by reduced food intake, dialysis treatment, comorbid conditions associated with aging, and chronic kidney disease (CKD).[36] Therefore, it is important to identify PEW, sarcopenia, and frailty when planning appropriate therapeutic interventions for hemodialysis patients.[37] There are several guidelines for assessing nutrition in hemodialysis patients. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) proposes different measures for monitoring nutritional status such as predialysis serum albumin levels, normalized protein equivalent of nitrogen appearance (nPNA), and subjective global assessment (SGA).[38] The European Best Practice Guidelines (EBPG) on nutrition emphasize the diagnosis of malnutrition through dietary assessment, SGA, technical investigations of body composition (BIA, DXA, near-infrared reactance), and measurement of BMI, nPNA, serum albumin, serum prealbumin, serum cholesterol.[39] The International Society of Renal Nutrition and Metabolism (ISRNM) defines PEW as a condition that meets three of the following four components: serum chemistry, body mass, muscle mass, and dietary intake.[6] In this study, we assessed nutritional status by measuring body composition, upper-arm circumference, albumin, cholesterol, and BMI. We also evaluated the hemoglobin, β2-microglobulin, ferritin, HbA1c, and CRP levels, which are known to reflect nutritional status.[40] Among these indicators, the GNRI was developed and validated to assesses the risk of malnutrition-related complications in the older adults.[23] Recently, GNRI has been used to evaluate various complications in hemodialysis patients.[1,13,22] The lower GNRI is related to a higher incidence of osteoporosis1, which was consistent with our study. We also found that sarcopenia in hemodialysis patients was associated with a lower GNRI. However, there Were no significant associations between cognitive impairment and GNRI.

Osteoporosis is one of the important complications in

Table 4. Baseline characteristics of participants with or without sarcopenia

Variables	Normal (N=114)	Presarcopenia + Sarcopenia (N=17)	*p*-value
Sex, male, n (%)	65 (57)	6 (35.3)	0.094
Cause of ESKD, n (%)			0.013
Diabetic	80 (70.2)	6 (35.3)	
Hypertensive	3 (2.6)	0 (0)	
Glomerulonephritis	6 (5.3)	3 (17.6)	
PCKD	5 (4.4)	0 (0)	
Other	3 (2.6)	2 (11.8)	
Unknown	17 (14.9)	6 (35.3)	
Diabetes, n (%)	83 (72.8)	6 (35.3)	0.002
GNRI, n (%)			0.010
Q1	24 (21.1)	9 (52.9)	0.013
Q2	31 (27.2)	4 (23.5)	1.000
Q3	29 (25.4)	4 (23.5)	1.000
Q4	30 (26.3)	0 (0)	0.012
Age (years)	65.5±10.5	71.0±9.7	0.066
Dialysis duration (months)	61.1±45.8	62.4±41.4	0.797
Femoral neck T-score	-1.83±1.21	-2.59±0.87	0.008
Lumbar spine T-score	-0.86±1.52	-1.99±1.55	0.005
Hemoglobin (g/dL)	11.0±1.0	11.1±0.7	0.569
LDL-cholesterol (mg/dL)	79.5±27.2	90.3±35.2	0.279
Triglyceride (mg/dL)	123±115	103±55	0.740
HDL-cholesterol (mg/dL)	47.9±15.2	58.6±24.1	0.069
ß2-microglobulin (mg/L)	19.4±5.4	21.0±7.2	0.755
Serum ferritin (μg/L)	350±247	333±397	0.220
HbA1c	6.37±1.17	5.92±0.97	0.109
Hs-CRP	3.55±6.86	5.15±10.45	0.201
Intact PTH (pg/mL)	189±137	247±221	0.485
Albumin (g/dL)	3.94±0.36	3.84±0.28	0.281
Body mass index (kg/m^2)	23.7±3.3	21.0±2.9	0.002
Upper arm circumference (cm)	24.7±3.5	22.1±2.0	<0.001
Appendicular muscle mass index (kg/m^2)	7.73±1.17	5.69±0.74	<0.001
MoCA total score	22.6±4.5	21.8±4.1	0.327

GNRI: geriatric nutrition risk index; ESKD: end-stage kidney disease; PCKD: polycystic kidney disease; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; intact PTH: intact parathyroid hormone; MoCA total score: Montreal cognitive assessment total score.

All data are expressed as means±SD.

hemodialysis patients.[2] In this study, long durations of dialysis and high intact PTH levels as nutritional indicators were associated with osteoporosis. These results are in line with those of the second phase of the Dialysis Outcomes and Practice Patterns Study (2002-2004), which showed that PTH levels are associated with an elevated risk of new fractures over long durations of dialysis.[5] CKD-MBD could contribute to the worsening of osteoporosis with PTH levels increasing.[41] The relationship between intact PTH level and nutritional status remains unclear, but a close association between muscle strength and nutrition has been suggested. Wright et al. explained that a higher intact PTH level increases the intermuscular adipose tissue of the forearm and calf.[42] An increased amount of intermuscular adipose tissue causes poor muscle strength;[43] thus, appropriate management of hyperparathyroidism might help prevent bone fracture and sarcopenia. In addition, a long duration of hemodialysis is associated with PEW, β2-microglobulin amyloidosis, and chronic uremic osteodystrophy, contributing to osteoporosis and related musculoskeletal symptoms.[44,45]

Sarcopenia, defined as the loss of muscle mass and muscle strength, is associated with various medical conditions.[25,46] The incidence of sarcopenia in hemodialysis patients varies widely from 3.9% to 63.3%.[47] One of the major risk factors for sarcopenia is malnutrition, which is affected by the duration of dialysis, diabetes, and phosphorus intake.18 In this study, the high incidence of sarcopenia was associated with high HbA1c levels. Insulin resistance in diabetes is associated with increased uremic myopathy and increased muscle protein degradation.[48] Therefore, careful glucose control might be beneficial for preventing muscle wasting in diabetic patients on hemodialysis. In our study, a higher GNRI quartile was associated with a lower frequency of sarcopenia, which is consistent with the findings of Tominaga et al., who suggested that increasing the GNRI improves the lean mass index.[13]

Sarcopenia is also closely linked to osteoporosis; when osteoporotic fractures occur, physical activity decreases, which may raise the risk of sarcopenia.[18] Indeed, muscle-volume preservation is important for maintaining BMD.[5] Usually, patients with long durations of dialysis are more likely to have sarcopenia, which affects bone health.[49]

Although marginally significant in the multivariate analysis, the lumbar spine T-score was negatively correlated with sarcopenia status. Moreover, the lower upper-arm circumference was related to poor nutritional status. Therefore, to prevent sarcopenia, it is essential to maintain proper nutritional status, perform physical exercise, and undergo therapies with anabolic hormones, anti-inflamma-

Table 5. Factors associated with (pre)sarcopenia in unadjusted and adjusted logistic models

Variables	Unadjusted model		Adjusted model†	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex, male	0.411 (0.142, 1.189)	0.101	0.557 (0.105, 2.964)	0.493
Diabetes	0.204* (0.069, 0.598)	0.004	0.052 (0.006, 0.428)	0.006
GNRI				
Q1	Reference		Reference	
Q2	0.344 (0.094, 1.253)	0.106	0.064* (0.005, 0.883)	0.040
Q3	0.368 (0.101, 1.344)	0.130	0.037 (0.001, 1.333)	0.071
Q4	-		-	-
Age (years)	1.824 (0.996, 3.342)	0.051	2.346 (1.011, 5.448)	0.047
Dialysis duration (months)	1.028 (0.621, 1.701)	0.913	-	-
Femoral neck T-score	0.461* (0.247, 0.861)	0.015	-	-
Lumbar spine T-score	0.452* (0.252, 0.810)	0.007	0.431 (0.162, 1.151)	0.093
Hemoglobin (g/dL)	1.156 (0.679, 1.967)	0.592	-	-
LDL-cholesterol (mg/dL)	1.419 (0.882, 2.281)	0.148	-	-
Triglyceride (mg/dL)	0.732 (0.310, 1.731)	0.478	-	-
HDL-cholesterol (mg/dL)	1.740* (1.083, 2.794)	0.022	-	-
ß2-microglobulin (mg/L)	1.303 (0.800, 2.122)	0.287	-	-
Serum ferritin (μg/L)	0.932 (0.541, 1.604)	0.800	-	-
HbA1c	0.642 (0.360, 1.146)	0.134	2.960* (1.033, 8.486)	0.043
Hs-CRP	1.189 (0.785, 1.801)	0.413	-	-
Intact PTH (pg/mL)	1.387 (0.891, 2.157)	0.146	-	-
Albumin (g/dL)	0.772 (0.472, 1.263)	0.303	3.728 (0.875, 15.888)	0.075
Body mass index (kg/m^2)	0.335* (0.159, 0.704)	0.003	1.355 (0.255, 7.194)	0.721
Upper arm circumference (cm)	0.441* (0.212, 0.918)	0.028	0.540 (0.275, 1.059)	0.073
MoCA total score	0.849 (0.516, 1.397)	0.520	-	-

GNRI: geriatric nutrition risk index; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; intact PTH: intact parathyroid hormone; MoCA total score: Montreal cognitive assessment total score.
†Model was adjusted for age, sex, body mass index, and diabetes
*$p<0.05$.

tory agents, and appetite stimulants.[50]

Cognitive impairment is common in hemodialysis patients.[19] Cognitive impairment negatively affects patient independence and medication compliance and causes behavioral symptoms.[51] Cognitive impairment shows different phenotypes depending on the underlying disease. Therefore, mild cognitive impairment can be distinguished between CKD patients and the general population.[52] The well-known causes of cognitive impairment in patients with CKD include the metabolic milieu of chronic inflammation, oxidative stress, uremia, and systemic vascular endothelial dysfunction.[53,54] In particular, ESKD patients also have several other contributors of dialysis-related cognitive dysfunction, including volume and electrolyte fluctuation, cerebral edema, cerebral hypoperfusion, intradialytic hypotension, excessive cytokine release, microembolism, and delirium.[55,56] There was no significant association between cognitive impairment and GNRI in our study, but anemia was significantly related to cognitive impairment. Marsh et al. also found better attention and executive function in ESKD patients with improved anemia.[57] The cutoff value of hemoglobin for preventing cognitive impairment is unknown. When we classified the patients with and without cognitive impairment, the mean hemoglobin level was 10.8±1.1 versus 11.1±0.8 g/dL. This finding was similar to the cognitive impairment cutoff criterion (haemoglobin <11 g/dL) in a study involving 338 ESKD patients.[15] The major causes of anemia in ESKD patients are poor erythropoietin production, lack of iron, and malnutrition.[58] Thus, to control anemia, erythropoietin-stimulating agents and iron supplements, as well as dietary control, are important. In this study, HGS and skeletal muscle mass index were lower in patients with cognitive impairment. Low muscle mass and strength could be recovered by exercise;[51] physical activity in hemodialysis patients also improves the vascular function by lowering systemic inflammation, oxidative stress, and arterial stiffness.[59] In addition, exercise promotes blood pressure, lipid, and glucose control. Through these pleiotropic effects, QOL and physical function can also be improved, and frailty risk can be reduced.[60]

This study has several limitations. First, we did not include all known nutritional variables because some biochemical tests related to nutritional status are expensive, poorly validated, or not available in the facility.[40] However, our study included representative variables that reflect the nutritional status of hemodialysis patients. Second, we defined sarcopenia based on muscle mass and muscle strength. The physical performance of the participants was not measured in our study. Nevertheless, there are studies defining sarcopenia without measuring physical performance.[1,10] Furthermore, recently updated sarcopenia definition proposed by the European working group on sarcopenia in older people (most widely cited definition) was based on low muscle strength and muscle quantity or quality.[61] Low physical performance is only used to define severe sarcopenia. Third, this is a single-center study with a small number of patients, so selection bias could have occurred; therefore, a larger multicenter study is recommended. Moreover, this study has a cross-sectional design; thus, longitudinal studies are required to assess the changes in the variables that are found to be significant. Fourth, we did not have data on educational and financial status and treatment with drugs to prevent dementia, which are

Table 6. Baseline characteristics of participants with cognitive impairment

Variables	Normal (N=77)	Cognitive impairment (N=54)	*p*-value
Sex, male, n (%)	51 (66.2)	20 (37)	0.001
Cause of ESKD, n (%)			0.704
Diabetic	49 (63.6)	37 (68.5)	
Hypertensive	1 (1.3)	2 (3.7)	
Glomerulonephritis	6 (7.8)	3 (5.6)	
PCKD	4 (5.2)	1 (1.9)	
Other	2 (2.6)	3 (5.6)	
Unknown	15 (19.5)	8 (14.8)	
Diabetes, n (%)	51 (66.2)	38 (70.4)	0.618
GNRI, n (%)			0.687
Q1	22 (28.6)	11 (20.4)	0.390
Q2	21 (27.3)	14 (25.9)	1.000
Q3	18 (23.4)	15 (27.8)	0.714
Q4	16 (20.8)	14 (25.9)	0.632
Age (years)	62.9±9.9	71.0±9.6	<0.001
Dialysis duration (months)	56.5±41.6	68.0±49.2	0.119
Femoral neck T-score	-1.73±1.15	-2.21±1.22	0.023
Lumbar spine T-score	-0.87±1.65	-1.22±1.44	0.209
Hemoglobin (g/dL)	11.1±0.8	10.8±1.1	0.323
LDL-cholesterol (mg/dL)	79.0±26.3	83.7±31.3	0.647
Triglyceride (mg/dL)	119±122	123±89	0.300
HDL-cholesterol (mg/dL)	48.8±17.4	50.0±16.2	0.665
ß2-microglobulin (mg/L)	20.1±6.3	18.9±4.6	0.252
Serum ferritin (µg/L)	342±227	357±322	0.640
HbA1c	6.23±1.12	6.44±1.2	0.278
Hs-CRP	3.57±7.84	4.01±6.78	0.662
Intact PTH (pg/mL)	211±155	175±142	0.214
Albumin (g/dL)	3.94±0.38	3.89±0.31	0.322
Handgrip strength (kg)	22.6±8.0	17.5±6.2	<0.001
Body mass index (kg/m^2)	22.8±3.3	24.0±3.3	0.042
Upper arm circumference (cm)	24.4±3.6	24.4±3.4	0.126
Appendicular muscle mass index (kg/m^2)	7.66±1.36	7.19±1.21	0.042

GNRI: geriatric nutrition risk index; ESKD: end-stage kidney disease; PCKD: polycystic kidney disease; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; intact PTH: intact parathyroid hormone; MoCA total score: Montreal cognitive assessment total score.

All data expressed as means±SD.

commonly investigated in other studies. Nevertheless, our study has many strengths. First, unlike previous Asian studies, which applied European guidelines, we considered our study to have adopted more appropriate guidelines as we diagnosed sarcopenia using Asian guidelines. Second, we were able to comprehensively understand the complications caused by malnutrition by using an organic approach to exploring osteoporo-
sis, sarcopenia, and cognitive impairment, all of which can occur as a complication of malnutrition in hemodialysis patients.

Conclusions

Hemodialysis patients are more common among the older adults. Both old age and long-term hemodialysis can lead to malnutrition, either on its own or indirectly as a result of related factors. This study revealed that inadequate nutrition was associated with the risk of osteoporosis and sarcopenia, but not cognitive impairment in hemodialysis patients. These comorbidities might diminish QOL and increase mortality. It is, therefore, important to understand the nutritional status of aging hemodialysis patients as well as to maintain proper nutrition in these patients. Further research is needed to improve the screening, assessment, maintenance, and improvement of nutritional status in hemodialysis patients.

AUTHOR DISCLOSURES

All authors declare no conflicts of interest.

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REFERENCES

1. Chen SC, Chung WS, Wu PY, Huang JC, Chiu YW, Chang JM, Chen HC. Associations among Geriatric Nutrition Risk Index, bone mineral density, body composition and handgrip strength in patients receiving hemodialysis. Nutrition. 2019; 65:6-12. doi: 10.1016/j.nut.2019.02.013.
2. Nitta K, Yajima A, Tsuchiya K. Management of osteoporosis in chronic kidney disease. Intern Med. 2017;56:3271-6. doi: 10.2169/internalmedicine.8618-16.
3. Di Iorgi N, Maruca K, Patti G, Mora S. Update on bone density measurements and their interpretation in children and adolescents. Best Pract Res Clin Endocrinol Metab. 2018;32: 477-98. doi: 10.1016/j.beem.2018.06.002.
4. Kwon YE, Choi HY, Kim S, Ryu DR, Oh HJ, ESRD Registry Committee of the Korean Society of Nephrology. Fracture risk in chronic kidney disease: A Korean population-based cohort study. Kidney Res Clin Pract. 2019;38:220-8. doi: 10. 23876/j.krcp.18.0099.
5. Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL et al. Incidence and risk factors for hip or other

Table 7. Factors associated with cognitive impairment

Variables	Unadjusted model		Adjusted model†	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex, male	0.3* (0.145, 0.62)	0.001	0.346 (0.144, 0.832)	0.018
Diabetes	1.211 (0.571, 2.566)	0.618	1.197 (0.473, 3.032)	0.704
GNRI				
Q1	Reference			
Q2	1.333 (0.495, 3.590)	0.569		
Q3	1.667 (0.615, 4.515)	0.315		
Q4	1.750 (0.632, 4.848)	0.282		
Age (years)	2.507* (1.610, 3.904)	<0.001	2.957 (1.764, 4.957)	<0.001
Dialysis duration (months)	1.293 (0.906, 1.846)	0.156		
Femoral neck T-score	0.644* (0.438, 0.947)	0.025		
Lumbar spine T-score	0.796 (0.557, 1.136)	0.208		
Hemoglobin (g/dL)	0.733 (0.508, 1.058)	0.098	0.585* (0.360, 0.950)	0.030
LDL-cholesterol (mg/dL)	1.180 (0.833, 1.673)	0.350	1.506 (0.943, 2.404)	0.087
Triglyceride (mg/dL)	1.043 (0.738, 1.474)	0.808		
HDL-cholesterol (mg/dL)	1.071 (0.756, 1.517)	0.698		
ß2-microglobulin (mg/L)	0.809 (0.564, 1.161)	0.251		
Serum ferritin (μg/L)	1.056 (0.747, 1.494)	0.755		
HbA1c	1.200 (0.845, 1.703)	0.307		
Hs-CRP	1.061 (0.751, 1.498)	0.736		
Intact PTH (pg/mL)	0.773 (0.529, 1.129)	0.183	0.663 (0.410, 1.074)	0.095
Albumin (g/dL)	0.862 (0.607, 1.224)	0.407		
Handgrip strength (kg)	0.438* (0.279, 0.688)	<0.001		
Body mass index (kg/m^2)	1.449* (1.011, 2.076)	0.043	1.667 (1.071, 2.602)	0.024
Upper arm circumference (cm)	1.005 (0.708, 1.425)	0.976		
Skeletal muscle mass index (kg/m^2)	0.685* (0.473, 0.991)	0.045		

GNRI, geriatric nutrition risk index; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; intact PTH, intact parathyroid hormone; MoCA total score, Montreal cognitive assessment total score
†Model was adjusted for age, sex, body mass index, and diabetes
*p<0.05.

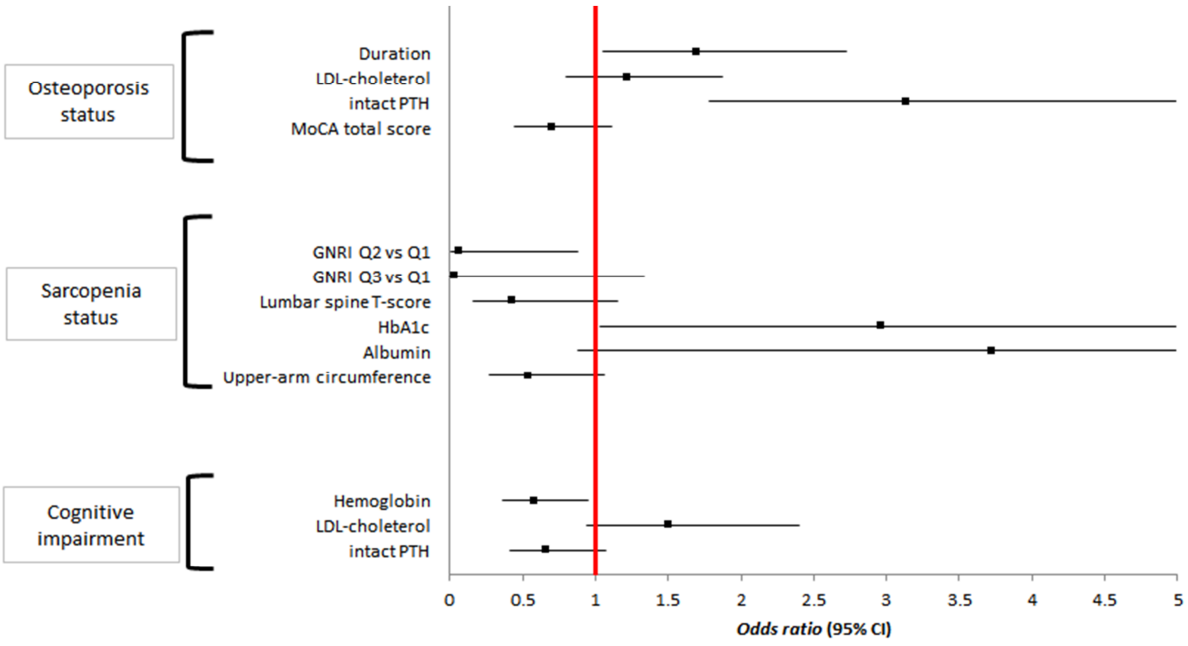

Figure 2. Factors associated with osteoporosis, sarcopenia, and cognitive impairment. Independent risk factors were evaluated using multivariate logistic regression analysis with stepwise backward selection. The independent risk factors were as follows: for osteoporosis, dialysis duration and intact parathyroid hormone (PTH); for sarcopenia, Geriatric Nutrition Risk Index (GNRI) quartile 2 vs. quartile 1 and hemoglobin A1c (HbA1c) level; for cognitive impairment, hemoglobin level. MoCA: Montreal Cognitive Assessment.

bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2006;70: 1358-66. doi: 10.1038/sj.ki.5001754.
6. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391-8. doi: 10.1038/sj.ki.5002585.
7. Hanna RM, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting,

sarcopenia, and cachexia in patients with chronic kidney disease. Blood Purif. 2019:1-10. doi: 10.1159/000504240.
8. Tournadre A, Vial G, Capel F, Soubrier M, Boirie Y. Sarcopenia. Joint Bone Spine. 2019;86:309-14. doi: 10.1016/j.jbspin.2018.08.001.
9. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. Clin Nutr. 2007;26:389-99. doi: 10.1016/j.clnu.2007.03.008.
10. Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, Kim HJ, Song YR. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. Clin Nutr. 2014;33:64-8. doi: 10.1016/j.clnu.2013.04.002.
11. Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Barany P, Heimburger O, Cederholm T, Stenvinkel P, Carrero JJ. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. Clin J Am Soc Nephrol. 2014;9:1720-8. doi: 10.2215/CJN.10261013.
12. Greco EA, Pietschmann P, Migliaccio S. Osteoporosis and sarcopenia increase frailty syndrome in the elderly. Front Endocrinol (Lausanne). 2019;10:255. doi: 10.3389/fendo.2019.00255.
13. Tominaga H, Oku M, Arishima Y, Ikeda T, Ishidou Y, Nagano S et al. Association between bone mineral density, muscle volume, walking ability, and geriatric nutritional risk index in hemodialysis patients. Asia Pac J Clin Nutr. 2018;27:1062-6. doi: 10.6133/apjcn.052018.03.
14. Dauncey MJ. Nutrition, the brain and cognitive decline: insights from epigenetics. Eur J Clin Nutr. 2014;68:1179-85. doi: 10.1038/ejcn.2014.173.
15. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S et al. Cognitive impairment in hemodialysis patients is common. Neurology. 2006;67:216-23. doi: 10.1212/01.wnl.0000225182.15532.40.
16. Drew DA, Weiner DE, Tighiouart H, Scott T, Lou K, Kantor A et al. Cognitive function and all-cause mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2015;65:303-11. doi: 10.1053/j.ajkd.2014.07.009.
17. Chang YT, Wu HL, Guo HR, Cheng YY, Tseng CC, Wang MC, Lin CY, Sung JM. Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases. Nephrol Dial Transplant. 2011;26:3588-95. doi: 10.1093/ndt/gfr013.
18. Ren H, Gong D, Jia F, Xu B, Liu Z. Sarcopenia in patients undergoing maintenance hemodialysis: incidence rate, risk factors and its effect on survival risk. Ren Fail. 2016;38: 364-71. doi: 10.3109/0886022X.2015.1132173.
19. Sarnak MJ, Tighiouart H, Scott TM, Lou KV, Sorensen EP, Giang LM et al. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. Neurology. 2013;80:471-80. doi: 10.1212/WNL.0b013e318 27f0f7f.
20. van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, de Vet HC. Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting. Clin Nutr. 2014;33:39-58. doi: 10.1016/j.clnu.2013. 04.008.
21. Cereda E, Limonta D, Pusani C, Vanotti A. Geriatric nutritional risk index: a possible indicator of short-term mortality in acutely hospitalized older people. J Am Geriatr Soc. 2006;54:1011-2. doi: 10.1111/j.1532-5415.2006.00754.x.
22. Kobayashi I, Ishimura E, Kato Y, Okuno S, Yamamoto T, Yamakawa T, Mori K, Inaba M, Nishizawa Y. Geriatric Nutritional Risk Index, a simplified nutritional screening index, is a significant predictor of mortality in chronic dialysis patients. Nephrol Dial Transplant. 2010;25:3361-5. doi: 10.1093/ndt/gfq211.
23. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L, Aussel C. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr. 2005;82:777-83. doi: 10.1093/ajcn/82.4.777.
24. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc. 2014;15:95-101. doi: 10.1016/j.jamda.2013.11.025.
25. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23. doi: 10.1093/ageing/afq034.
26. Ling CH, de Craen AJ, Slagboom PE, Gunn DA, Stokkel MP, Westendorp RG, Maier AB. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clin Nutr. 2011;30:610-5. doi: 10.1016/j.clnu.2011.04.001.
27. Lee SY, Ahn S, Kim YJ, Ji MJ, Kim KM, Choi SH, Jang HC, Lim S. Comparison between dual-energy X-ray absorptiometry and bioelectrical impedance analyses for accuracy in measuring whole body muscle mass and appendicular skeletal muscle mass. Nutrients. 2018;10:738. doi: 10.3390/nu10060738.
28. Furstenberg A, Davenport A. Comparison of multifrequency bioelectrical impedance analysis and dual-energy X-ray absorptiometry assessments in outpatient hemodialysis patients. Am J Kidney Dis. 2011;57:123-9. doi: 10.1053/j.ajkd.2010.05.022.
29. Arai H, Akishita M, Chen LK. Growing research on sarcopenia in Asia. Geriatr Gerontol Int. 2014;14(Suppl 1):1-7. doi: 10.1111/ggi.12236.
30. Izawa KP, Watanabe S, Oka K, Mogamiya T, Tada M, Nakata S et al. Differences in physical performance based on the Geriatric Nutritional Risk Index in elderly female cardiac patients. Aging Clin Exp Res. 2015;27:195-200. doi: 10.1007/s40520-014-0264-5.
31. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-9. doi: 10.1111/j.1532-5415.2005.53221.x.
32. Lam B, Middleton LE, Masellis M, Stuss DT, Harry RD, Kiss A, Black SE. Criterion and convergent validity of the Montreal cognitive assessment with screening and standardized neuropsychological testing. J Am Geriatr Soc. 2013;61:2181-5. doi: 10.1111/jgs.12541.
33. Angermann S, Baumann M, Steubl D, Lorenz G, Hauser C, Suttmann Y et al. Cognitive impairment in hemodialysis patients: Implementation of cut-off values for the Montreal Cognitive Assessment (MoCA)-test for feasible screening. PLoS One. 2017;12:e0184589. doi: 10.1371/journal.pone.0184589.
34. van Loon IN, Wouters TR, Boereboom FT, Bots ML, Verhaar MC, Hamaker ME. The relevance of geriatric impairments in patients starting dialysis: a systematic review. Clin J Am Soc Nephrol. 2016;11:1245-59. doi: 10.2215/ CJN.06660615.
35. Vandewoude MF, Alish CJ, Sauer AC, Hegazi RA. Malnutrition-sarcopenia syndrome: is this the future of nutrition screening and assessment for older adults? J Aging Res. 2012;2012:651570. doi: 10.1155/2012/651570.
36. Atlantis E, Martin SA, Haren MT, Taylor AW, Wittert GA, Florey Adelaide Male Aging S. Lifestyle factors associated with age-related differences in body composition: the Florey

Adelaide Male Aging Study. Am J Clin Nutr. 2008;88:95-104. doi: 10.1093/ajcn/88.1.95.
37. Rodrigues J, Cuppari L, Campbell KL, Avesani CM. Nutritional assessment of elderly patients on dialysis: pitfalls and potentials for practice. Nephrol Dial Transplant. 2017;32: 1780-9. doi: 10.1093/ndt/gfw471.
38. Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2001;37:S66-70. doi: 10.1053/ajkd.2001.207 48.
39. Fouque D, Vennegoor M, ter Wee P, Wanner C, Basci A, Canaud B et al. EBPG guideline on nutrition. Nephrol Dial Transplant. 2007;22(Suppl 2):ii45-87. doi: 10.1093/ndt/ gfm020.
40. Pfeiffer CM, Lacher DA, Schleicher RL, Johnson CL, Yetley EA. Challenges and lessons learned in generating and interpreting NHANES nutritional biomarker data. Adv Nutr. 2017;8:290-307. doi: 10.3945/an.116.014076.
41. Tanaka S, Ito M. Bone and nutrition. Nutrition care of renal osteodystrophy. Clin Calcium. 2015;25:1057-62.
42. Wright CS, Laing EM, Pollock NK, Hausman DB, Weaver CM, Martin BR et al. Serum 25-hydroxyvitamin D and intact parathyroid hormone influence muscle outcomes in children and adolescents. J Bone Miner Res. 2018;33:1940-7. doi: 10. 1002/jbmr.3550.
43. Buford TW, Lott DJ, Marzetti E, Wohlgemuth SE, Vandenborne K, Pahor M, Leeuwenburgh C, Manini TM. Age-related differences in lower extremity tissue compartments and associations with physical function in older adults. Exp Gerontol. 2012;47:38-44. doi: 10.1016/j. exger.2011.10.001.
44. Scarpioni R, Ricardi M, Albertazzi V, De Amicis S, Rastelli F, Zerbini L. Dialysis-related amyloidosis: challenges and solutions. Int J Nephrol Renovasc Dis. 2016;9:319-28. doi: 10.2147/IJNRD.S84784.
45. Afifi WM, Abo Elsaoud AM, Elgawish MH, Ghorab AM. Musculoskeletal manifestations in end-stage renal disease patients on hemodialysis and relation to parathyroid dysfunction. Saudi J Kidney Dis Transpl. 2019;30:68-82.
46. Rosenberg IH. Sarcopenia: origins and clinical relevance. Clin Geriatr Med. 2011;27:337-9. doi: 10.1016/j.cger.2011. 03.003.
47. Lamarca F, Carrero JJ, Rodrigues JC, Bigogno FG, Fetter RL, Avesani CM. Prevalence of sarcopenia in elderly maintenance hemodialysis patients: the impact of different diagnostic criteria. J Nutr Health Aging. 2014;18:710-7. doi: 10.1007/s12603-014-0505-5.
48. Trierweiler H, Kisielewicz G, Jonasson TH, Petterle RR, Moreira CA, Borba VZC. Sarcopenia: a chronic complication of type 2 diabetes mellitus. Diabetol Metab Syndr. 2018;10:25. doi: 10.1186/s13098-018-0326-5.
49. Mekki K, Remaoun M, Belleville J, Bouchenak M. Hemodialysis duration impairs food intake and nutritional parameters in chronic kidney disease patients. Int Urol Nephrol. 2012;44:237-44. doi: 10.1007/s11255-010-9875-8.
50. Ikizler TA. Optimal nutrition in hemodialysis patients. Adv Chronic Kidney Dis. 2013;20:181-9. doi: 10.1053/j.ackd. 2012.12.002.
51. Martins CT, Ramos GS, Guaraldo SA, Uezima CB, Martins JP, Ribeiro Junior E. Comparison of cognitive function between patients on chronic hemodialysis who carry out assisted physical activity and inactive ones. J Bras Nefrol. 2011;33:27-30. doi:
52. Viggiano D, Wagner CA, Blankestijn PJ, Bruchfeld A, Fliser D, Fouque D et al. Mild cognitive impairment and kidney disease: clinical aspects. Nephrol Dial Transplant. 2020;35:10-7. doi: 10.1093/ndt/gfz051.
53. Berr C, Balansard B, Arnaud J, Roussel AM, Alperovitch A. Cognitive decline is associated with systemic oxidative stress: the EVA study. Etude du Vieillissement Arteriel. J Am Geriatr Soc. 2000;48:1285-91. doi: 10.1111/j.1532-5415. 2000.tb02603.x.
54. Seliger SL, Longstreth WT, Jr. Lessons about brain vascular disease from another pulsating organ, the kidney. Stroke. 2008;39:5-6. doi: 10.1161/STROKEAHA.107.496000.
55. Kalimo H. Does chronic brain edema explain the consequences of cerebral small-vessel disease? Stroke. 2003;34:806-12. doi: 10.1161/01.STR.0000062360.09018. F3.
56. Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. Semin Dial. 2009;22:636-43. doi: 10.1111/j.1525-139X.2009.00659.x.
57. Marsh JT, Brown WS, Wolcott D, Carr CR, Harper R, Schweitzer SV, Nissenson AR. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney Int. 1991;39:155-63. doi: 10.1038/ki.1991.20.
58. Mikhail A, Brown C, Williams JA, Mathrani V, Shrivastava R, Evans J, Isaac H, Bhandari S. Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease. BMC Nephrol. 2017;18:345. doi: 10.1186/s12882-017-0688-1.
59. Bronas UG. Exercise training and reduction of cardiovascular disease risk factors in patients with chronic kidney disease. Adv Chronic Kidney Dis. 2009;16:449-58. doi: 10.1053/j. ackd.2009.07.005.
60. Bronas UG, Puzantian H, Hannan M. Cognitive impairment in chronic kidney disease: vascular milieu and the potential therapeutic role of exercise. Biomed Res Int. 2017;2017: 2726369. doi: 10.1155/2017/2726369.
61. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48:16-31. doi: 10.1093/ageing/afy169.