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SARCOPENIA AND FRAILTY IN PD: IMPACT ON MORTALITY, MALNUTRITION, AND INFLAMMATION

Yuka Kamijo,[1,2] Eiichiro Kanda,[2,3] Yoshitaka Ishibashi,[1] and Masayuki Yoshida[2]

Department of Nephrology,[1] Japanese Red Cross Medical Center, Tokyo, Japan; Department of Life Science and Bioethics,[2] Graduate School of Medicine, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan; and Department of Nephrology,[3] Tokyo Kyosai Hospital, Meguro-ku, Tokyo, Japan

♦ ***Background:*** **It is known that sarcopenia is related to malnutrition-inflammation-atherosclerosis (MIA) syndrome and is an important problem in dialysis patients. The notion of frailty includes various physical, psychological, and social aspects. Although it has been reported that sarcopenia is associated with poor prognosis in patients with hemodialysis, reports on peritoneal dialysis (PD) patients are rare. In this study, we examined the morbidity and mortality of sarcopenia and frailty in PD patients. We also investigated the MIA-related factors.**

♦ ***Methods:*** **We evaluated 119 patients cross-sectionally and longitudinally. The Asian Working Group for Sarcopenia criteria and the Clinical Frailty Scale (CFS) were used to diagnose sarcopenia and frailty. The primary outcome is all-cause mortality with sarcopenia and frailty. The secondary outcome is the relationship between various MIA-related factors.**

♦ ***Results:*** **Morbidity of sarcopenia and frailty in PD patients was 8.4% and 10.9%, respectively. Old age, high values of Barthel Index, Charlson Comorbidity Index, CFS, and low values of body mass index (BMI), muscle strength, muscle mass, and slow walking were associated with sarcopenia. Interleukin-6, albumin, and prealbumin were significantly correlated with muscle mass. During follow-up, the presence of sarcopenia or frailty was associated with the risk of mortality. In multivariate analysis, CFS was related to the mortality rate of PD patients.**

♦ ***Conclusions:*** **The presence of sarcopenia or frailty was associated with a worse prognosis.**

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KEY WORDS: Peritoneal dialysis; clinical frailty scale; MIA syndrome; dialysis in elderly.

In Japan, elderly people over the age of 65 account for 26.7% of the population, indicating that the country is currently experiencing an unprecedented aging society (1). Moreover, the proportion of elderly people continues to increase, expected to reach 39.9% by 2060. This means that 1 in every 2.5 people will be over 65 years old while the overall population will decrease, and the number of people who require nursing care will increase rapidly. In 2013, 67% of dialysis patients were over 65 years old (2). As dialysis patients become older, complications stemming from nutritional disorders become more common, with a reported prevalence of 30 – 60%, and these are more serious in older patients (3,4). Various pathologies related to malnutrition have been reported as factors that deeply affect both life prognosis and quality of life (QOL); hence, such pathologies represent important issues that need to be addressed in relation to the aging of chronic kidney disease (CKD) patients and dialysis patients (5). It has been reported that malnutrition in CKD patients progresses gradually, with a deterioration in renal function seen at an early stage prior to the introduction of renal replacement therapy (RRT) (6). There are several factors related to this, including decreased dietary intake, accumulation of uremic substances, catabolic effects of RRT, oxidative stress, metabolic and hormonal imbalances, increased insulin resistance, systemic inflammation, and comorbid conditions. This complex entanglement of factors leads to a decrease in energy sources and muscle mass, which is conceptualized as sarcopenia, frailty, states of muscle mass reduction, and physical, social, and mental deterioration. These conditions are known to correlate with each other as a disease concept related to malnutrition (7,8). Frailty is an age-related disorder of multiple bio-functions, including nutritional status, physical ability, mobility, social activity, cognitive function, and psychological aspect, as well as a state that is associated with a higher risk of adverse outcomes, such as a decline in functional ability, increased falls, delirium, institutionalization, hospitalization, and death (9). When introducing dialysis, approximately 80% of patients have been reported as showing signs of frailty, including pre-frailty (10). Taking countermeasures against frailty at an early stage may alleviate decreased QOL and the degree of care associated with elderly dialysis patients, which is also important in terms of the allocation of urgent medical resources. There are several studies of frailty in peritoneal dialysis (PD) patients though the difference from hemodialysis (HD) remains unclear (11,12). Although the effects on the prognosis of HD patients have recently been reported, reports on sarcopenia in PD patients remain rare, and there are relatively few reports concerning the correlation between sarcopenia and frailty (13,14).

Correspondence to: Yuka Kamijo, Department of Nephrology, Japanese Red Cross Medical Center, 4-1-22, Hiroo Shibuya-Ku, Tokyo 150-8935, Japan.
kamijo_yuka@med.jrc.or.jp
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While sarcopenia focuses on the deterioration of physical functions accompanying aging, especially in dialysis (15), frailty focuses more on the functional aspects of social life, cognitive function, activities of daily living, as well as physical function. In clinical practice, cooperation with physical therapists is important for sarcopenia. Meanwhile, in frailty, it is also important to build a wider cooperation system, such as with psychiatrists, psychologists, neurologists, care managers, visiting nurses, and families.

In the current study, we aimed to evaluate whether sarcopenia and frailty have a negative impact on mortality in PD patients. We also investigated the morbidity of sarcopenia and frailty, and assessed the factors related to disease conditions, such as malnutrition-inflammation-atherosclerosis (MIA) syndrome.

MATERIALS AND METHODS

STUDY DESIGN, SETTING, AND PARTICIPANTS

The current prospective cohort study was conducted at the Japanese Red Cross Medical Center's Peritoneal Dialysis Unit. At the beginning of the research period, the surveyed population satisfied the following inclusion criteria: 1) patients had initiated PD at least 2 months prior to recruitment; 2) patients were over 20 years old. Patients characterized by 1) any acute disorders or infectious diseases; 2) hospitalization; or 3) recent major surgery were excluded. The morbidity of sarcopenia and frailty, as well as the relationship between various MIA-related factors and sarcopenia, were examined at the beginning of the follow-up period. Furthermore, during the follow-up period, we investigated the mortality of sarcopenia and frailty patients.

The study was approved by the Ethics Committee of the Japanese Red Cross Medical Center (No. 763), and it fully complies with the provisions of the Declaration of Helsinki. Informed consent was obtained from all individual participants.

DATA COLLECTION AND FOLLOW-UPS

The study started with registration on 1 April 2016. We received informed consent from patients and then conducted each examination and followed up until 31 October 2017.

All analyzed data concerning the 119 participating patients were extracted from the information database that was created by the Japanese Red Cross Medical Center in Japan. Blood tests, a physical examination relevant to sarcopenia and protein energy wasting (PEW), cardiac echocardiography, and a body fluid volume test were conducted in addition to peritoneal function and dialysis adequacy tests. Furthermore, various evaluations regarding the social life aspect were also completed periodically.

The following basic data were recorded for all participants at baseline: age, gender, height, weight, body mass index (BMI), comorbidity conditions, and duration of PD. We also collected the plasma concentrations of hemoglobin (Hb), albumin (Alb), prealbumin (PRAB), interleukin-6 (IL6), and C-reactive protein (CRP). The IL6 levels were measured using an enzyme-linked immunosorbent assay (ELISA). The normalized protein equivalent nitrogen appearance (nPNA) was calculated using the methods described by Randerson *et al.* and then normalized to the actual weight (16). Residual renal function was calculated as the average of the 24-hour urinary urea while the dialysis adequacy was measured by the total (renal and peritoneal) weekly urea clearance (wKt/V). The muscle mass and body fluid volume (overhydration [OH]) were measured using a whole-body multi-frequency bioelectrical impedance analysis (BIA) device (Body Composition Monitor-BCM; Fresenius Medical Care, Germany) (17). Data regarding the Mini-Mental State Examination (MMSE), Barthel Index (BI), performance status (PS), Clinical Frailty Scale (CFS), Charlson Comorbidity Index (CCI), and walking speed were also collected. All the participants received follow-up until the end of the study period, death or administrative censoring (including renal transplantation, switching to hemodialysis, transfer to another PD center, loss to follow-up, and withdrawal of treatment).

The primary outcome of the study is all-cause mortality in PD patients with sarcopenia and frailty. The secondary outcome is the determination of the morbidity of sarcopenia and frailty in PD patients, as well as the relationship between various MIA-related factors.

DIAGNOSIS OF SARCOPENIA

According to the diagnostic algorithm provided by the Asian Working Group for Sarcopenia (AWGS), sarcopenia was diagnosed based on the following criteria: 1) low muscle mass; 2) weak muscle strength (handgrip strength); and/or 3) poor physical function (slow walking) (8).

The appendicular skeletal muscle mass (ASM) was calculated as the sum of the skeletal muscle in the patient's arms and legs. The relative skeletal muscle mass index (SMI) was defined as the ASM divided by the height in meters, squared. Low muscle mass was classified as an SMI score of less than 7.0 kg/m^2 and 5.7 kg/m^2 in men and women, respectively.

Muscle strength was assessed by grip strength, which was measured using a dynamometer (GRIP-D; Takei Ltd, Japan). The participants were asked to exert maximum effort twice using their dominant hand, and the average value was used for the analysis. Low handgrip strength was defined as < 26 kg and < 18 kg for males and females, respectively.

The usual walking speed (m/s) on a 10-meter course was used as an objective measure of physical performance; a slow walking speed was defined as slower than 0.8 m/s.

ASSESSMENT OF FRAILTY

There are a variety of tools that can be used to assess frailty, with each tool serving a distinct purpose. The CFS, which uses clinical descriptors and pictographs, was developed to provide clinicians with an easily applicable tool for stratifying older

adults according to their level of vulnerability, and it was validated to be a strong predictor of both institutionalization and mortality (18,19). In the current study, the assessments, which were conducted by 2 clinical physicians, took place during regular medical examinations, and they involved chart reviews and face-to-face assessments with patients and families. The CFS was scored from 1 (very fit) to 9 (terminally ill). Frailty was assessed based on the CFS descriptions: non-frailty (scores of 1 – 4) and mild to severe frailty (scores of 5 – 8). Participants with a CFS score of 9 were excluded from the analysis because they are considered terminally ill rather than frail.

STATISTICAL ANALYSIS

The results were expressed as mean ± standard deviation (SD) for the continuous variables, median and interquartile range (IQR) for the skewed distributions, and number of patients and percentages for the categorical variables. Any differences in the participants' characteristics related to their sarcopenia and frailty status were analyzed using a 2-sample *t*-test, a χ^2 test, and the Mann-Whitney test. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. A logarithmic transformation was applied to the IL6 and CRP data in all the analyses because these data did not present a normal distribution. The multivariate logistic regression model was used to adjust the factors related to sarcopenia, including age, sex, CCI, BMI, nPNA, and CFS. Box plots were used to show the distribution of the inflammatory and nutritional markers in the 2 groups. Spearman's correlation coefficient was used to assess the associations between the logarithm (ln) CRP, logarithm (ln) IL6, and sarcopenia-related variables. We used the Kaplan-Meier curve and log-rank test to compare the mortality rates in patients with sarcopenia and frailty. Furthermore, we performed a Cox proportional hazards regression analysis that examined age, gender, SMI, muscle strength, walking speed, and CFS. Two-sided probability values of < 0.05 were considered statistically significant. All statistical analyses were conducted using R version 3.2.4.

RESULTS

PARTICIPANTS

From 130 initially screened patients, a total of 119 consecutive patients were enrolled in this prospective observational study. A flowchart according to the STROBE recommendations is shown in Figure 1. We excluded 11 patients because they were hospitalized or undergoing less than 2 months of PD treatment. Among the included patients, the mean age ± standard deviation of the participants was 66.8 ± 13.2 years, 84 (70.6%) were male, and 21.0% had diabetes. Eleven patients were lost during the follow-up period: 7 died during this period while 4 dropped out because of a change in their dialysis method, 1 of whom had a transplant and 3 transitioned to HD.

PREVALENCE OF SARCOPENIA AND FRAILTY

The prevalence of sarcopenia and frailty by age (in decades) is shown in Figure 2. Thirteen participants (10.9%) were identified as being affected by sarcopenia; among these, 11 (13.1%) were male and 2 (5.7%) were female, and 8 (61.5%) were judged to be sarcopenic because of a low gait speed (n = 1, 7.7%; female) or poor grip strength (n = 7, 53.8%; all male), whereas 5 (38.4%, 4 males and 1 female) exhibited the concomitant presence of reduced muscle strength and slow gait speed.

Ten participants (8.4%) were identified as being affected by frailty; 7 (8.3%) were male and 3 (8.5%) were female. The participants' CFS scores ranged from 1 (very fit) to 7 (severe frailty), with the mean ± SD CFS score being 3.14 ± 1.08 and a median of 3.

The distribution of patients based on their individual CFS scores is displayed in Figure 2, which shows there was no ceiling or flooring effect for the scores. The CFS is subjective, so different clinicians may have graded severity differently or classified patients according to different criteria. However, this is a more realistic reflection of routine clinical practice, which often requires an overall clinical impression. In the current study, evaluation was carried out by 2 physicians in charge of the patient.

Collapsing the CFS categories resulted in 109 patients with CFS scores ranging from 1 – 4 (non-frailty), 7 patients with CFS scores ranging from 5 – 6 (mild to moderate frailty), and 3 patients with CFS scores ranging from 7 – 8 (severe frailty). The former category was classified as the non-frailty group while the latter 2 categories were combined into the frailty group. Among them, 8 participants (53.8% of the sarcopenia group and 87.5% of the frailty group) had both sarcopenia and frailty, 5 (38.4% of the sarcopenia group) only had sarcopenia, and 2 (12.5% of the frailty group) only had frailty (Table 1).

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE SARCOPENIA AND FRAILTY GROUPS

Table 2 presents the clinical characteristics of the participants according to the presence of sarcopenia. The participants

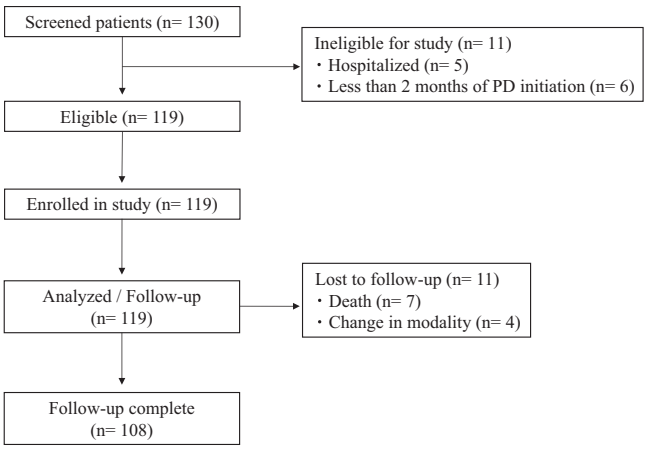

Figure 1 — STROBE diagram of patient flow through the study. PD = peritoneal dialysis.

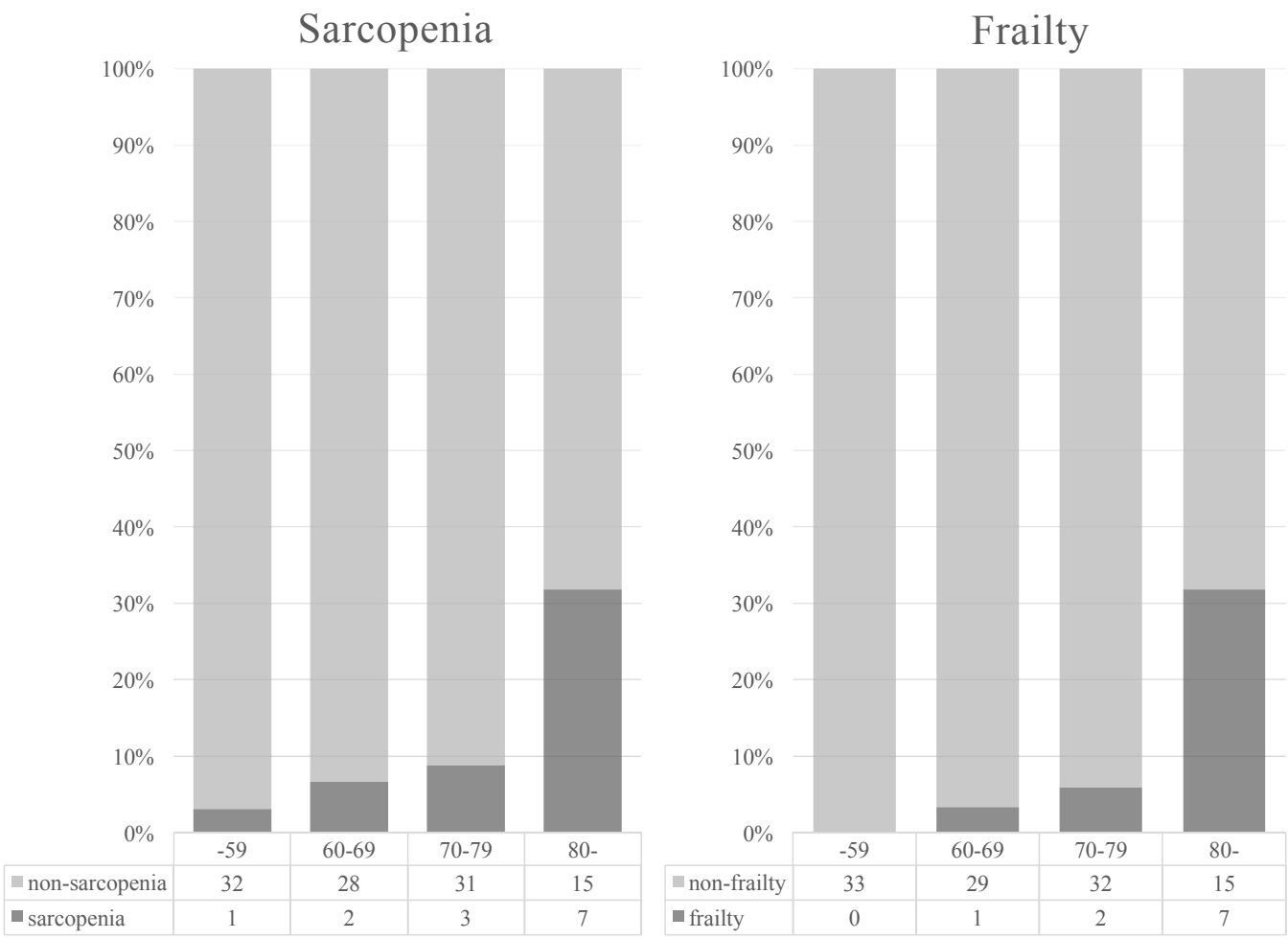

Figure 2 — Prevalence of sarcopenia (left) and frailty (right) according to age decades.

TABLE 1
Number (Percentage) of Patients and Prevalence of Sarcopenia and Frailty

	Sarcopenia	Non-Sarcopenia	Total
Severe frailty	3 (23.0%, 100.0%)	0	3
Mild-moderate frailty	5 (38.4%, 71.4%)	2 (1.8%, 28.5%)	7
Non-frailty	5 (38.4%, 4.5%)	104 (98.1%, 95.4%)	109
Total	13	106	119

with sarcopenia were more likely to be older. Furthermore, they had higher BI and CFS values ($p < 0.001$) and a statistically significant lower BMI, SMI, handgrip strength, and usual walking speed when compared with the participants without sarcopenia. However, no significant difference was observed in the distributions between the groups based on sex, systolic and diastolic blood pressure, the presence of diabetes, CCI, nPNA, duration of PD, residual renal function, dialysis efficiency, body fluid volume, or cognitive function.

However, the participants with frailty were more likely to be older, have higher BI and CCI values, and have lower PS values ($p < 0.001$). The participants with frailty exhibited significantly lower SMI, handgrip strength, and usual walking speed. Although the cognitive function was marginally not significant, the MMSE tended to be low in the frailty group ($p = 0.051$) (Table 2).

According to the multivariate logistic regression model, after adjusting for age, sex, BMI, nPNA, CCI, and CFS, sarcopenia was significantly correlated with the CFS (adjusted odds ratio: 12.2) (Table 3).

INFLAMMATORY AND NUTRITIONAL MARKERS ACCORDING TO SARCOPENIA STATUS

In terms of the inflammatory and nutritional markers, the sarcopenia group showed significantly low Alb and PRAB values, as well as elevated IL6 values, whereas the frailty group showed significantly low Alb and PRAB values and elevated IL6 and CRP values, suggesting malnutrition and inflammation (Table 4). The levels of ln-IL6 were inversely associated with

TABLE 2
Characteristics of Study Participants According to the Presence of Sarcopenia and Frailty

	Non-sarcopenia	Sarcopenia	*P* value	Non-frailty	Frailty	*P* value
Age (years)	65.3±12.9	79.2±9.39	<0.001[c]	65.4±12.8	82.5±7.11	<0.001[c]
Male (*n*, %)	74 (69.8%)	10 (76.9%)	0.835	77 (70.6%)	7 (70.0%)	0.998
DM (*n*, %)	23 (21.7%)	2 (15.4%)	0.868	22 (20.2%)	3 (30.0%)	0.746
CCI	3.0 (2.0–4.0)	4.0 (2.0–5.0)	0.127	2.0 (2.0–4.0)	5.0 (5.0–5.75)	0.001[b]
Duration of PD (weeks)	158.5 (76.6–282)	137.8 (32.1–210)	0.441	162.1 (78.0–324)	70.5 (25.2–131)	0.029[a]
BMI (kg/m^2)	22.2 (20.0–25.4)	20.3 (18.6–22.4)	0.044[a]	22.1 (20.0–25.2)	21.1 (19.6–23.9)	0.358
SBP (mmHg)	132.9±21.7	125.4±28.4	0.257	132.8±22.7	124.4±19.6	0.257
DBP (mmHg)	74.6±15.9	70.4±17.9	0.382	74.6±16.1	68.5±15.6	0.247
Renal wKt/V	0.24 (0–0.87)	0.44 (0–0.64)	0.993	0.24 (0–0.86)	0.53 (0.13–0.98)	0.398
Total wKt/V	1.87 (1.64–2.18)	1.9 (1.73–2.03)	0.912	1.87 (1.64–2.18)	1.92 (1.74–2.01)	0.871
D/P_{cr}	0.57±0.1	0.63±0.09	0.056	0.57±0.1	0.62±0.09	0.105
OH (L)	1.3 (0.5–2.08)	0.8 (0.30–2.00)	0.493	1.2 (0.5–2.00)	1.4 (0.48–2.08)	0.954
nPNA (g/kg/day)	0.7 (0.6–0.85)	0.68 (0.63–0.8)	0.986	0.7 (0.6–0.85)	0.67 (0.64–0.79)	0.924
MMSE	29 (27–30)	28 (25.2–30)	0.648	29 (27–30)	26 (24–28)	0.051
Performance Status	1.0 (1.0–1.0)	1.0 (1.0–2.0)	<0.001[c]	1.0 (1.0–1.0)	2.0 (2.0–2.75)	<0.001[c]
Barthel Index	100 (100–100)	95 (72.5–100)	<0.001[c]	100 (100–100)	90 (65.0–95.0)	<0.001[c]
CFS	2.92±0.72	5.0±1.53	<0.001	2.90±0.67	5.80±0.92	<0.001
SMI	7.44 (6.81–8.77)	6.42 (5.36–6.71)	<0.001[c]	7.41 (6.71–8.64)	6.55 (5.28–6.81)	<0.001[c]
Grip strength (kg)	24.6 (19.2–31.1)	19 (16.1–21.7)	0.042[a]	24.6 (19.2–31.2)	16.4 (13.9–20.5)	0.006[b]
Walk speed (m/s)	1.68±0.50	1.18±0.64	0.007[b]	1.67±0.51	0.79±0.30	0.001[b]

DM = diabetes mellitus; CCI = Charlson comorbidity index; PD = peritoneal dialysis; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; wKt/V = weekly Kt/V; D/P_{cr} = dialysate to plasma creatinine ratio; OH = overhydration; nPNA = normalized protein equivalent nitrogen appearance; MMSE = Mini-Mental State Examination; CFS = clinical frailty scale; SMI = relative skeletal muscle mass index; SD = standard deviation.
Values expressed as mean±SD, median (interquartile range), or number (percent).
[a] $p<0.05$.
[b] $p<0.01$.
[c] $p<0.001$.

SMI (r = -0.23, $p = 0.012$) while the levels of Alb and PRAB were also positively correlated with SMI (r = 0.441, $p < 0.001$, and r = 0.354, $p < 0.001$, respectively)

ASSOCIATION OF SARCOPENIA AND FRAILTY WITH MORTALITY

During the follow-up period, 7 participants (5.9%) died. Cardiovascular complications accounted for 28.5% of the deaths, including acute myocardial infarction and sudden cardiac death. The remaining causes of death were acute pancreatitis, respiratory tract infection, and aspiration pneumonia. The mean follow-up period was 589.2 days. The survival rate for 500 days was 0.667 vs 0.971 (sarcopenic vs non-sarcopenic, $p < 0.001$) and 0.441 vs 0.981 (frailty vs non-frailty, $p < 0.001$). We analyzed each mortality rate in patients over 65 years as a post-hoc analysis. Of the 74 patients over 65 years old, there were 12 sarcopenic and 10 frailty patients. The survival rate was 0.636 vs 0.951 (sarcopenic vs non-sarcopenic, $p < 0.001$) and 0.444 vs 0.968 (frailty vs non-frailty, $p < 0.001$) (Figure 3). In the Cox regression analysis, after adjustments were made for potential confounders, such as age, sex, walking speed, SMI, and grip strength, the CFS remained an independent predictor of mortality ($p < 0.05$) (Table 5).

TABLE 3
Multivariate Logistic Regression Model Associated with Sarcopenia

Univariate	Adjusted OR	95% CI	*P* value
Age	1.03	0.92–1.14	0.586
Male	2.49	0.18–32.7	0.489
CCI	0.5	0.20–1.25	0.137
BMI	0.77	0.55–1.08	0.131
nPNA	0.49	0.002–84.2	0.786
CFS	12.2	2.27–65.5	0.003[a]

OR = odds ratio; CI = confidence interval; CCI = Charlson comorbidity index, BMI = body mass index; nPNA = normalized protein equivalent nitrogen appearance; CFS = Clinical Frailty Scale.
The risk factor for sarcopenia adjusted by age, gender, CCI, BMI, nPNA, and CFS.
[a] $p<0.01$.

DISCUSSION

The main finding of the current study was the demonstration of the prevalence of sarcopenia and frailty in patients

TABLE 4
Inflammatory and Nutritional Markers According to the Presence of Sarcopenia and Frailty

	Non-sarcopenia	Sarcopenia	*P* value	Non-frailty	Frailty	*P* value
Hb (g/dL)	11.6±1.27	12.3±1.79	0.055	11.7±1.37	±1.11	0.57
Alb (g/dL)	3.47±0.46	3.12±0.44	0.009[b]	3.48±0.45	±0.37	<0.001[c]
PRAB (mg/dL)	38.4±9.85	29.8±5.71	0.003[b]	38.3±9.78	±5.93	0.004[b]
Ln CRP (mg/dL)	-1.92±1.24	-1.12±1.28	0.03[a]	0.28±0.33	1.12±1.45	<0.001[c]
Ln IL6 (pg/mL)	1.52±0.73	2.24±0.59	0.001[b]	1.58±0.74	2.45±0.57	0.002[b]

Hb = hemoglobin; Alb = albumin; PRAB = prealbumin; Ln CRP = logarithm CRP; Ln IL6 = logarithm interleukin-6; SD = standard deviation.
Values expressed as mean±SD, median (interquartile range).
[a] $p<0.05$.
[b] $p<0.01$.
[c] $p<0.001$.

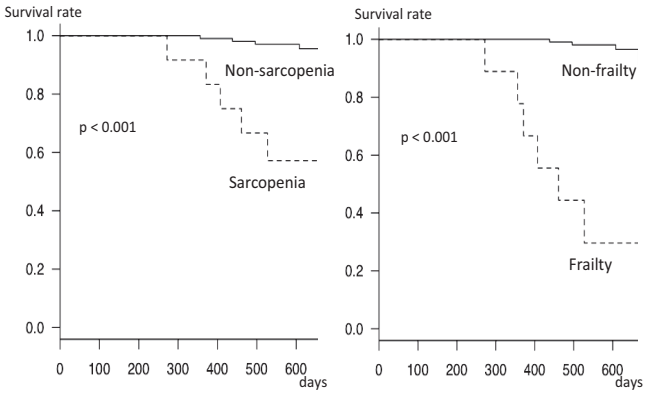

Figure 3 — Kaplan survival analysis of survival associated with the presence of sarcopenia and frailty in PD patients. PD = peritoneal dialysis.

TABLE 5
Multivariate Cox Proportional Hazards Model

Univariate	Adjusted HR	95% CI	*P* value
Age	1.15	0.95–1.38	0.156
Male	0.08	0.002–3.28	0.183
SMI	1.90	0.74–4.89	0.183
Grip strength	0.95	0.77–1.17	0.63
Walking speed	19.3	0.82–454.1	0.066
CFS	9.83	1.80–53.7	0.008[a]

HR = hazards ratio; CI = confidence interval; SMI = skeletal muscle mass index; CFS = Clinical Frailty Scale.
The risk factor for mortality adjusted by age, gender, walking speed, SMI, grip strength, and CFS.
[a] $p<0.01$.

undergoing PD, suggesting that patients with sarcopenia or frailty have a lower survival rate. We also observed that the analyzed inflammatory and nutritional markers are associated with both sarcopenia and frailty.

To the best of our knowledge, this is the first study to evaluate mortality associated with sarcopenia in PD patients. Sarcopenia is considered an important geriatric condition that can be a precursor to the development of frailty, late-life disability, decreased QOL, and a higher mortality rate in elderly individuals (20).

In the present study, sarcopenia was found to be present in 10.9% of PD patients. This prevalence is consistent with the prevalence previously reported for CKD stage 3 and HD patients (21,22). It has been suggested that advanced CKD is a condition associated with a process of accelerated aging and that the effect of various CKD-associated catabolic and chronic inflammation alterations may explain why sarcopenia is such a prominent typical feature in CKD and even more serious in end-stage renal disease (ESRD) (23). Considering the fact that the prevalence of sarcopenia increases as CKD becomes more serious, it is reasonable to assume that the prevalence found for PD patients in the current study was lower than the prevalence previously reported for HD patients.

We have demonstrated there is an association between sarcopenia and clinical variables using malnutrition and inflammation markers. Our results indicate that there is a trend toward higher levels of ln-IL6 and lower levels of Alb and PRAB in patients with sarcopenia and frailty. We also observed inverse associations between the ln-IL6 levels and muscle mass, as well as positive correlations between Alb, PRAB, and muscle mass. It has been well described that oxidative stress and increased levels of inflammatory mediators represent possible mechanisms contributing to the pathogenesis of sarcopenia (24). Increased levels of inflammatory cytokines, such as IL6 and TNF-alpha, have been found to be associated with sarcopenia in both the general population and patients with ESRD (25).

We also diagnosed frailty using the CFS, which is easy to apply and clinical applicability is validated (18,19). The CFS is a subjective measure of a patient's overall health status as determined by the clinician's judgment. The clinician considers perceived functional impairments (mobility and cognitive function) and comorbid conditions to assign a level of frailty to the patient (18). As a result, we determined the correlation with the total mortality after a multivariate adjustment. The current study showed frailty to have a prevalence of 8.4% in

patients with PD, allowing the determination of some associated factors. Patients with frailty are more likely to be older and exhibit higher BI and CCI values, as well as lower PS, SMI, handgrip strength, and usual walking speed values. Our findings are comparable with those of Alfaadhel *et al.*, who, in a cohort of patients undergoing dialysis, observed an increase in the risk of death with each 1-point increase in the CFS and found that 26% of patients had CFS scores ≥ 5 (11). Although their population was considerably younger (average age of 63 years vs 66.8 in the current study), the participants in their study were almost all HD patients (77%). In addition to facility and race differences, the current study only targeted PD patients, which is one reason why the prevalence of frailty was lower in our study when compared with Alfaadhel *et al.*'s research. Although the difference between PD and HD remains unclear, several reports have suggested a possible cause for the lower prevalence of frailty in PD patients. In patients with PD, residual kidney function tends to be maintained, and PD patients are reported to have higher QOL than HD patients (26). Recently, Neumann *et al.* observed in a longitudinal study that PD patients are less likely to have cognitive impairment than HD patients (27).

Furthermore, we showed that the sarcopenic group, defined by a reduced muscle mass index according to the BIA in combination with reduced grip strength and walking speed, was associated with all-cause death; undergoing PD and having frailty as defined by the CFS was also associated with all-cause mortality. After adjustments were made for potential confounders, including age, CFS, gender, walking speed, SMI, and grip strength, the CFS remained an independent predictor of mortality. This showed that a single factor did not modify the association between frailty and outcome. This finding is similar to the findings of previous studies, suggesting that frailty as a complex factor (including social and cognitive aspects) is most related to loss of life among patients undergoing dialysis (11,12). Recently, a meta-analysis was reported that showed loneliness is a risk factor for all-cause mortality (28). Hakulinen *et al.* reported social isolation as a risk factor for myocardial infarction, stroke, and death. Gale *et al.* reported that loneliness exacerbates frailty (29,30). Based on these findings, it seems prudent to suggest that the treatment options for PD patients should target comprehensive care, including muscle functionality, cognitive function, nutrition, and social activity.

Our study has some limitations. First, there may be unknown or unmeasured confounders because of the observational and single-center nature of the study. However, we were able to adjust for several important variables that have been shown to be associated with mortality. Second, the current study used a cross-sectional approach in addition to a longitudinal approach, meaning that we could not show causal relationships.

CONCLUSION

We demonstrated the morbidity of sarcopenia and frailty in PD patients. We also showed that they were associated with the risk of mortality, malnutrition, and inflammation markers.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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