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Association between sarcopenia and frailty in elderly patients with chronic kidney disease

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Abstract

Background Frailty and sarcopenia are prevalent in chronic kidney disease (CKD) populations and could increase the risk for adverse health outcomes. Few studies assess the correlation between frailty, sarcopenia and CKD in non-dialysis patients. Therefore, this study aimed to determine frailty-associated factors in elderly CKD stage I–IV patients, expected to early identify and intervene in the frailty of elderly CKD patients.

Methods A total of 774 elderly CKD I–IV patients (>60 years of age) recruited from 29 clinical centers in China between March 2017 and September 2019 were included in this study. We established a Frailty Index (FI) model to evaluate frailty risk and verified the distributional property of FI in the study population. Sarcopenia was defined according to the criteria of the Asian Working Group for Sarcopenia 2019. Multinomial logistic regression analysis was used to assess the associated factors for frailty.

Results Seven hundred seventy-four patients (median age 67 years, 66.0% males) were included in this analysis, with a median estimated glomerular filtration rate of 52.8 mL/min/1.73 m^2. The prevalence of sarcopenia was 30.6%. The FI exhibited a right-skewed distribution. The age-related slope of FI was 1.4% per year on a logarithmic scale ($r^2 = 0.706$, 95% CI 0.9, 1.8, $P < 0.001$). The upper limit of FI was around 0.43. The FI was related to mortality (HR = 1.06, 95% CI 1.00, 1.12, $P = 0.041$). Multivariate multinomial logistic regression analysis showed that sarcopenia, advanced age, CKD stage II–IV, low level of serum albumin and increased waist–hip ratio were significantly associated with high FI status, while advanced age and CKD stage III–IV were significantly associated with for median FI status. Moreover, the results from the subgroup were consistent with the leading results.

Conclusions Sarcopenia was independently associated with an increased risk for frailty in elderly CKD I-IV patients. Patients with sarcopenia, advanced age, high CKD stage, high waist–hip ratio and low serum albumin level should be assessed for frailty.

Keywords Frailty; Frailty Index; Sarcopenia; Chronic Kidney Disease; Elderly

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Introduction

Frailty is an age-related clinical syndrome characterized by the reduced physiological reserve of several organ systems and worse adaptability to stressors such as acute disease or trauma.[1] Frailty encompasses several multisystem derangements, which means that there is no single diagnostic tool or biomarker available to identify the presence and extent of frailty. At present, the most widely used principal models to operationalize the frailty concept are the Fried Frailty Phenotype[2] and the Rockwood Frailty Index (FI).[3] Frailty Phenotype was developed by Fried in which three or more criteria were present: unintentional weight loss, self-reported exhaustion, weakness (low grip strength), slow walking speed and low physical activity.[2] Frailty Index, defined by Rockwood as the proportion of accumulated deficits (symptoms, signs, functional impairments and laboratory abnormalities),[3] made a more comprehensive, multidimensional assessment of frailty, reflecting the different degrees of frailty. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death.[4] There are ethnic differences in muscle mass. Previous studies have suggested that compared with Whites, Asians tend to have lower BMI, skeletal muscle mass, muscle strength and fat mass [S1-S3], which emphasizes the need for ethnic-specific diagnostic criteria for sarcopenia. Under normal conditions, the rate of new muscle cell formation, hypertrophy and protein loss maintains a delicate balance. This balance is coordinated by the nervous, endocrine and immune systems and is also affected by nutritional status and physical activity.[5] An overactive and unregulated inflammation characterized by frailty can over-activate the decomposition of muscle, resulting in the loss of muscle quality and strength, accompanied by the decline of muscle function. Therefore, the causal relationship between frailty and sarcopenia has not been apparent.

Chronic kidney disease (CKD) is a worldwide public health problem. The prevalence of CKD in the general population is approximately 11–16%.[6] Elderly patients are prone to diabetes, hypertension, cardiovascular and cerebrovascular diseases, and other underlying diseases, and the high possibility of drug treatment and surgical treatment, which increase the prevalence of CKD.[7] Elderly patients with CKD are prone to decline in physical and cognitive function, depression, malnutrition, osteoporosis and frailty [S4-S9]. Compared with young patients, elderly patients with CKD are also prone to death or cardiovascular complications rather than ESRD.[8] Epidemiologic studies demonstrated that sarcopenia and frailty are prevalent in dialysis and non-dialysis CKD populations [S10-S12]. Both sarcopenia and frailty could increase the risk for adverse health outcomes such as disability, fall, hospitalization, institutionalization and death.[3,9] With disease progression, the body composition constantly changes in patients with CKD. The loss of kidney metabolism and function, as well as the activation of pathways leading to chronic low-grade inflammation, metabolic acidosis, accumulation of uremic toxins, anorexia and endocrine abnormalities, which proceed along with the progression of CKD, might aggravate protein catabolism,[10] leading to loss of muscle mass and strength. Restricted activity during dialysis and fatigue after dialysis shortens the time for physical activity, which impairs muscle function.[11] Meanwhile, both haemodialysis and peritoneal dialysis procedures stimulate protein degradation, reduce protein synthesis and persist following dialysis,[12,13] leading to a loss of muscle mass. Importantly, nephrologists frequently encounter patients infirmed by multiple co-morbidities who present with features consistent with sarcopenia and frailty, while sarcopenia and frailty are not routinely assessed in the clinical practice of nephrology. It is of great significance to improve the evaluation of sarcopenia and frailty in patients with CKD.

There were few studies on the correlation between sarcopenia and frailty of elderly patients with CKD in China, especially non-dialysis patients. Previous studies on frailty primarily defined frailty by Fried Frailty Phenotype, which is physical frailty. Few studies defined frailty by FI, including physical and psychosocial deficits. We conducted a Chinese observational prospective study of ageing population with chronic kidney disease(C-OPTION). The baseline data, including Frailty Index and sarcopenia, were obtained. In this study, we aimed to assess the associated factors of frailty and explore the association between frailty and sarcopenia, expected to help identify and intervene in frailty in Chinese hospitalized elderly CKD I-IV patients.

Method

Study participants

This multicentre, cross-sectional, observational study was a baseline data analysis of the Chinese observational prospective study of the ageing population with chronic kidney disease(C-OPTION), with the aim to investigate the frailty of elderly CKD stage I–IV patients in China. This study involved elderly CKD I-IV patients ($>$60 years of age) recruited from 29 clinical centres in China between March 2017 and September 2019. All of these clinical centres were renal departments from different hospitals. All the participants conformed to the following inclusion criteria: aged $\geq$ 60 years old, received a diagnosis of CKD stage I–IV.[14] We excluded participants if they (1) had received dialysis or renal transplantation; (2) were diagnosed with acute kidney injury; (3) were suffered from active or metastatic tumours within 24 months; (4) had severe heart failure (New York Heart Association function class III or IV); (5) had HIV infection; (6)

had isolated haematuria; and (7) were unable to communicate with examiners, unable to complete the study procedure even if assisted or otherwise unable to comply with the study protocol. CKD was diagnosed as follows: a history of CKD for more than 3 months; estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2 or albumin-to-creatinine ratio (ACR) more than 30 mg/g or proteinuria more than 150 mg/24 h. The CKD Epidemiology Collaboration (CKD-EPI) creatinine equation[15] was adopted to calculate eGFR. CKD stages were consistent with the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines.[14] This study was approved by the Ethics Committee of the Chinese PLA General Hospital (No. S2017-038-01). All participants signed informed consent before their inclusion in the study.

Frailty

In constructing a measure of frailty, we adopted a deficit accumulation approach.[3] We started by modifying a 37-item Frailty Index developed in the Systolic Blood Pressure Intervention Trial (SPRINT) based on items available in our cohort (30 items),[16] then added another five items available in our cohort similar to those included in the FI applied to the Hypertension in the Very Elderly Trial (HYVET) cohort[17] and the African American Health (AAH) cohort.[18] The proposed list of 35 total items and scoring scheme was described in Table S1. Our 35-item FI includes information on the Montreal Cognitive Assessment-Basic (MoCA-B) [S13], Geriatric Depression Scale-15 (GDS-15) [S14], self-ratings of health from Kidney Disease Quality of Life-36 (KDQOL-36) [S15], self-care ability from activities of daily living [S16], gait speed, smoking status, sleeping status, body mass index, laboratory measurements, BP measurements and self-reported comorbidities. The FI was calculated as the sum of each deficit, divided by the total number of non-missing items. We weighted each item equally and excluded participants who did not have at least 30 non-missing items (31 participants).

Sarcopenia

Newly introduced in Asian Working Group for Sarcopenia 2019, sarcopenia was defined as low muscle mass combined with low muscle strength or low physical performance.[19] Low muscle strength was defined according to handgrip strength (HGS $<$ 28 kg for men and $<$18 kg for women), low physical performance was defined according to gait speed (GS $<$ 1.0 m/s for both sexes), and low muscle mass was defined according to appendicular skeletal muscle mass index (ASMI $<$7.0 kg/m^2 for men and $<$5.7 kg/m^2 for women). Mid-upper arm circumference (MUAC $\leq$28.6 cm for men and $\leq$27.5 for women), which was strongly correlated with ASMI among older adults in China,[20] can be used to define low muscle mass in our cohort.

Other variables

Apart from variables included in the FI and sarcopenia, we collected data, including age, sex, white blood cell, percentage of neutrophils and lymphocyte, serum creatinine, cystatin C, serum albumin, parathyroid hormone (PTH), serum calcium, serum phosphorus, urinary protein excretion, triceps skinfold thickness (TSF) and waist–hip ratio (WHR).

Outcomes

To verify the reliability of the FI model, we analysed the survival of participants enrolled at the First Medical Center of the Chinese PLA General Hospital. The primary outcome was defined as all-cause death. The early and delayed visits allowance would be 1 month from the scheduled visit date. Patients who could not show up in hospitals on time were followed up by telephone call or online contact until death, withdrawal from the study, loss to follow-up or October 2021; $>$90% of the patients kept in touch during this period. All methods were performed under the relevant guidelines and regulations.

Statistical analyses

The average and 99th of FI were graphed against age; curves were fitted using an exponential function similar to previous publications.[21] We summarized baseline participant characteristics across groups of baseline FI. The variables were expressed as the median (interquartile, IQR) or number, percentage. As appropriate, groups were compared by the Mann–Whitney *U* test or χ^2 analysis. As there is no clinically significant FI cutoff value for frailty in this cohort, we evaluated FI in tertiles to allow for a better understanding of the relationship between frailty and variables. Age, gender, CKD stages, sarcopenia, WHR, TSF, 24 h proteinuria, serum albumin, cystatin C, parathyroid hormone, phosphorus and calcium were examined as covariates in univariate multinomial logistic regression analysis. Variables with a *P*-value $<$ 0.10 in univariate analysis and sex were selected for multivariate multinomial logistic regression. Survival analyses were done using univariate and multivariate Cox regression analyses with the FI as the independent variable and age, gender and CKD stages as covariates. Analyses were performed with IBM SPSS 22.0 software (SPSS Institute, IBM, USA). All *P*-values were two-sided. Statistical significance was set at the level of $P < 0.05$.

Results

Baseline characteristics of the patients

Altogether, 1051 Chinese elderly patients with CKD were enrolled in the study. Two hundred seventy-seven patients were excluded because they did not meet the eligibility criteria or complete the necessary inspections and tests. Finally, 774 patients were included in the study (Figure 1). One hundred ninety-three patients enrolled at the First Medical Center of the Chinese PLA General Hospital were followed up for a median of 36.5 months.

The clinical characteristics of the study patients were shown in Table 1. A total of 774 patients (median age 67 years, 66.0% males) from 29 clinics were included in this analysis with a median eGFR of 52.8 mL/min/1.73 m^2. Five hundred eighty-four (75.5%) patients had hypertension, 276 (35.7%) patients had diabetes, 123 (15.9%) patients had stroke and 237 (30.6%) patients had sarcopenia. The low FI tertile range was ≤0.17, the median FI tertile range from 0.17 to 0.25, and the high FI tertile range was ≥0.25. As presented in Table 1, we found a trend toward advanced age, lower eGFR, thicker waistline, faster GS, higher systolic blood pressure, a higher level of PTH, WBC and NE%, and a lower level of LYM% in the higher FI tertiles ($P < 0.05$). Patients in high FI tertile had the heaviest proteinuria, the highest levels of serum cystatin C, phosphorus and calcium, and the highest WHR and HGS ($P < 0.05$). Patients in low FI tertile had a higher percentage of CKD stage I while they had a higher percentage of CKD stage IV in median and high tertiles. Patients with CKD stage II or III were evenly distributed in each FI tertile. There were no significant differences between the FI tertiles in sex, muscle mass, DBP, hipline, TSF or MUAC.

Verify a Frailty Index model

In our study, the FI exhibited a right-skewed distribution (median = 0.20, interquartile range = 0.15, 0.27) (Figure 2). The FI observed a clear linear increase to age (on a logarithmic scale). A rate of deficits accumulation was 1.4% per year (r^2 = 0.706, 95% CI 0.9, 1.8, $P < 0.001$) with 99th of FI showed no relationship to age (r^2 = 0.002, P = 0.843) (Figure 3). The upper limit of FI was around 0.43. The FI was related to mortality in our cohort. During follow-up for a median of 36.5 months in Chinese PLA General Hospital, 6.7% (n = 13) of patients died. Age and FI were significant predictors of mortality both in the univariate and multivariable cox regression analysis. A 0.01 increase in FI was associated with a 6% increase in the risk of death (95% CI 1.00, 1.12, P = 0.041) (Table 2). The above results suggest that this Frailty Index can be used to evaluate the frailty of our cohort compared with previously published indexes.[21]

Factors associated with frailty

Frailty-associated factors were explored through multinomial logistic regression analysis. FI was analysed as a categorical variable. The low FI tertile was used as the reference group. Univariate logistic regression analysis showed that age, sarcopenia, CKD stages, WHR, proteinuria, serum levels of cystatin C, albumin, PTH, phosphorus, WBC, NE% and LYM% were associated with high FI status, and age, CKD stages, WHR, serum levels of cystatin C, PTH, WBC, NE% and LYM% were associated with median FI status in elderly patients with CKD stage I-IV (Table 3). Multivariate logistic regression analysis demonstrated that advanced age (OR = 1.08, 95% CI 1.04, 1.12, $P < 0.001$), sarcopenia (OR = 1.67, 95% CI 1.10, 2.53,

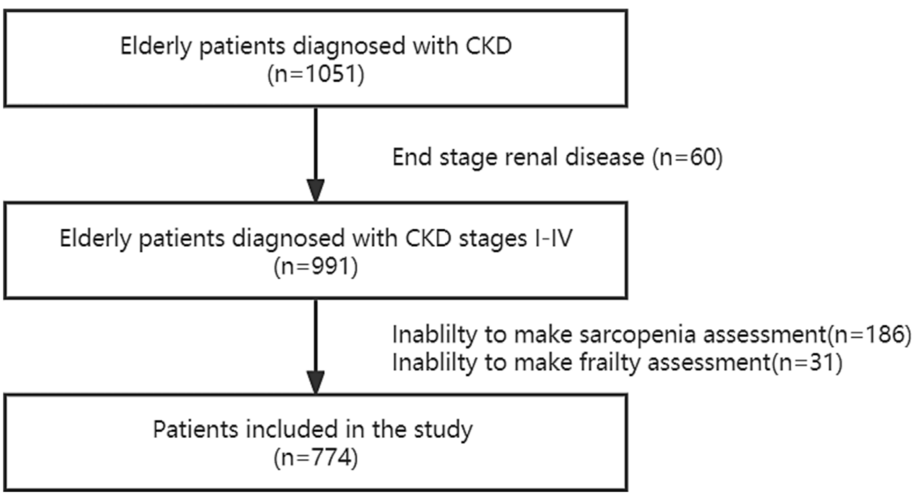

Figure 1 Patient flowchart.

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Table 1 Baseline characteristics of elderly patients with CKD

	FI ≤ 0.17 (*n* = 258)	0.17 < FI < 0.25 (*n* = 257)	FI ≥ 0.25 (*n* = 259)	Total cohort (*n* = 774)	*P*
Demographic data					
Age (year)	65 (63, 69)	68 (65, 72)*	68 (64, 74)*	67 (64, 72)	<0.001
Male (*n*, %)	171 (66.3)	174 (67.7)	166 (64.1)	511 (66.0)	0.683
Hypertension (*n*, %)	156 (60.5)	209 (81.3)*	219 (84.6)*	584 (75.5)	<0.001
Diabetes (*n*, %)	51 (19.8)	102 (39.7)*	123 (47.5)*	276 (35.7)	<0.001
Stroke	16 (6.2)	34 (13.2)*	73 (28.2)*,#	123 (15.9)	<0.001
Sarcopenia (*n*, %)	63 (24.4)	80 (31.1)*	94 (36.3)*	237 (30.6)	0.013
Stage of CKD					<0.001
Stage I (*n*, %)	70 (27.1)	40 (15.6)*	25 (9.7)*,#	135 (17.4)	
Stage II (*n*, %)	65 (25.2)	55 (21.4)	63 (24.3)	183 (23.6)	
Stage III (*n*, %)	90 (34.9)	101 (39.3)	94 (36.3)	285 (36.8)	
Stage IV (*n*, %)	33 (12.8)	61 (23.7)*	77 (29.7)*	171 (22.1)	
Anthropometric measurements					
SBP (mmHg)	130 (121, 142)	136 (125, 146)*	140 (128, 154)*,#	135 (124, 147)	<0.001
DBP (mmHg)	80 (73, 86)	80 (74, 88)	80 (73, 90)	80 (73, 88)	0.380
BMI (kg/m^2)					
Male	24.5 (22.6, 26.6)	25.8 (13.5, 17.9)*	25.2 (23.4, 27.7)*	25.1 (23.1, 27.5)	0.001
Female	24.8 (22.7, 27.1)	25.0 (23.1, 28.0)	25.8 (23.3, 27.5)	25.0 (23.0, 27.3)	0.256
HGS (kg)					
Male	33.3 (28.8, 40.2)	32.0 (27.3, 37.2)	28.9 (24.6, 35.4)*,#	31.5 (26.6, 37.7)	<0.001
Female	22.7 (19.0, 26.2)	22.0 (18.7, 25.1)	20.2 (16.7, 24.3)*,#	21.7 (17.8, 25.1)	0.038
WHR	0.94 (0.90, 0.97)	0.94 (0.90, 0.98)	0.95 (0.91, 0.98)*	0.94 (0.91, 0.98)	0.032
TSF (cm)	1.50 (1.10, 2.30)	1.70 (1.20, 2.40)	1.70 (1.20, 2.37)	29.0 (26.5, 31.0)	0.211
MUAC (cm)					
Male	29.0 (26.5, 30.7)	29.3 (27.0, 31.0)	29.0 (26.0, 31.7)	28.5 (26.0, 31.0)	0.658
Female	28.7 (26.0, 31.0)	28.0 (26.0, 31.5)	28.7 (26.0, 30.3)	1.70 (1.20, 2.31)	0.958
GS	1.0 (0.8, 1.2)	0.8 (0.7, 1.1)*	0.8 (0.6, 1.0)*	0.9 (0.7, 1.1)	<0.001
Laboratory parameters					
24 h proteinuria (g/24 h)	1.60 (0.49, 3.23)	1.96 (0.53, 3.48)	2.78 (1.00, 4.81)*,#	2.20 (0.56, 3.70)	<0.001
eGFR (mL/min/1.73 m^2)	62.2 (42.1, 91.3)	48.8 (32.6, 76.9)*	46.7 (27.2, 69.2)*	52.8 (33.9, 82.0)	<0.001
Cystatin C (mg/L)	1.41 (1.04, 1.92)	1.71 (1.19, 2.25)*	1.87 (1.37, 2.50)*,#	1.65 (1.15, 2.25)	<0.001
Albumin (g/L)	36.7 (28.9, 40.9)	37.0 (29.5, 41.8)	33.7 (25.1, 39.0)*,#	36.0 (27.1, 40.8)	<0.001
PTH (pg/mL)	40.37 (26.00, 61.95)	49.98 (32.93, 77.45)*	48.89 (28.39, 76.80)*	45.46 (28.14, 70.69)	0.001
Serum phosphorus (mmol/L)	1.14 (1.04, 1.25)	1.17 (1.03, 1.32)	1.20 (1.07, 1.33)*	1.18 (1.04, 1.30)	0.005
Serum calcium (mmol/L)	2.20 (2.06, 2.32)	2.22 (2.08, 2.32)	2.15 (2.01, 2.29)*,#	2.19 (2.05, 2.31)	0.010
WBC (×10^9/L)	6.07 (5.04, 7.59)	6.76 (5.48, 8.15)*	6.87 (5.41, 8.43)*	6.56 (5.33, 8.07)	0.001
NE (%)	59.1 (53.1, 66.3)	63.4 (57.1, 70.3)*	63.6 (55.7, 70.2)*	62.1 (55.0, 69.3)	<0.001
LYM (%)	30.2 (23.3, 36.8)	25.9 (20.1, 30.9)*	26.1 (20.4, 32.7)*	27.2 (21.1, 33.7)	<0.001

Baseline characteristics of elderly patients with CKD according to tertiles of the Frailty Index. Median (interquartile) for non-normal distribution variables, number (%) for category variables.
BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GS, gait speed; HGS, handgrip strength; LYM, lymphocyte; MUAC, mid-upper arm circumference; NE, neutrophils; PTH, parathyroid hormone; SBP, systolic blood pressure; TSF, triceps skinfold thickness; WBC, white blood cell; WHR, waist-hip-ratio.
*Low FI tertile as reference group, $P < 0.05$.
#Median FI tertile as reference group, $P < 0.05$.

P = 0.016), CKD stage II-IV ($OR_{CKD\ stage\ II}$ = 2.36, 95% CI 1.26, 4.42, P = 0.007; $OR_{CKD\ stage\ III}$ = 2.12, 95% CI 1.08, 4.23, P = 0.030; $OR_{CKD\ stage\ IV}$ = 3.17, 95% CI 1.21, 8.35, P = 0.019), low level of serum albumin (OR = 0.97, 95% CI 0.94, 0.99, P = 0.012) and increased WHR (OR = 1.03, 95% CI 1.00, 1.07, P = 0.030) were significantly associated with high FI status, while only advanced age (OR = 1.06, 95% CI 1.02, 1.10, P = 0.005) and CKD stage III-IV ($OR_{CKD\ stage\ III}$ = 1.90, 95% CI 1.00, 3.61, P = 0.049; $OR_{CKD\ stage\ IV}$ = 3.00, 95% CI 1.13, 7.94, P = 0.027) were significantly associated with median FI status (Table 4). There was no statistical significance in sarcopenia between low FI and median FI patients in neither univariate nor multivariate logistic regression analysis (OR = 1.40, 95% CI 0.95, 2.06, P = 0.09; OR = 1.43, 95% CI 0.95, 2.16, P = 0.086).

Subgroup analysis of the association between frailty and sarcopenia in serum albumin groups

There was a significant interaction between sarcopenia and serum albumin ($P < 0.05$). No statistically significant interaction between sarcopenia and other variables (age, CKD stage and WHR). The interaction between sarcopenia and serum albumin was further explored by dividing the cohort into two groups according to albumin levels (<35 g/L, ≥35 g/L) and repeating the fully-adjusted analysis within these subgroups (Table 5). There was a strong, statistically significant association between sarcopenia and frailty in the <35 g/L group ($OR_{median\ FI\ tertile}$ 2.28, 95% CI 1.19, 4.35, P = 0.013; $OR_{high\ FI\ tertile}$ 3.40, 95% CI 1.80, 6.43, P = 0.001), but not in another subgroup.

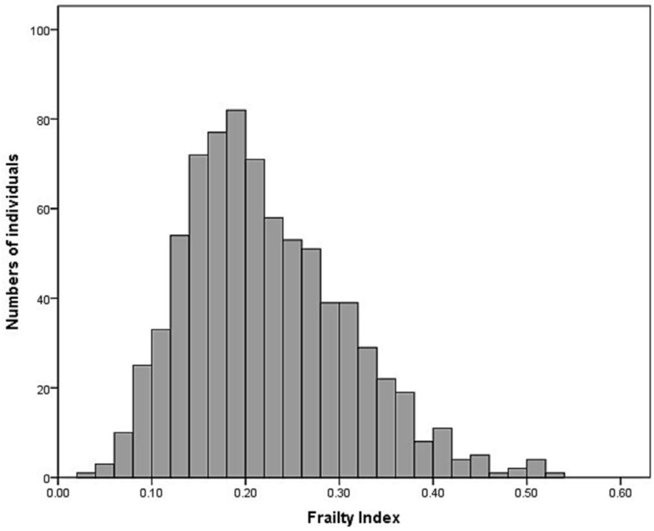

Figure 2 Frailty Index distribution.

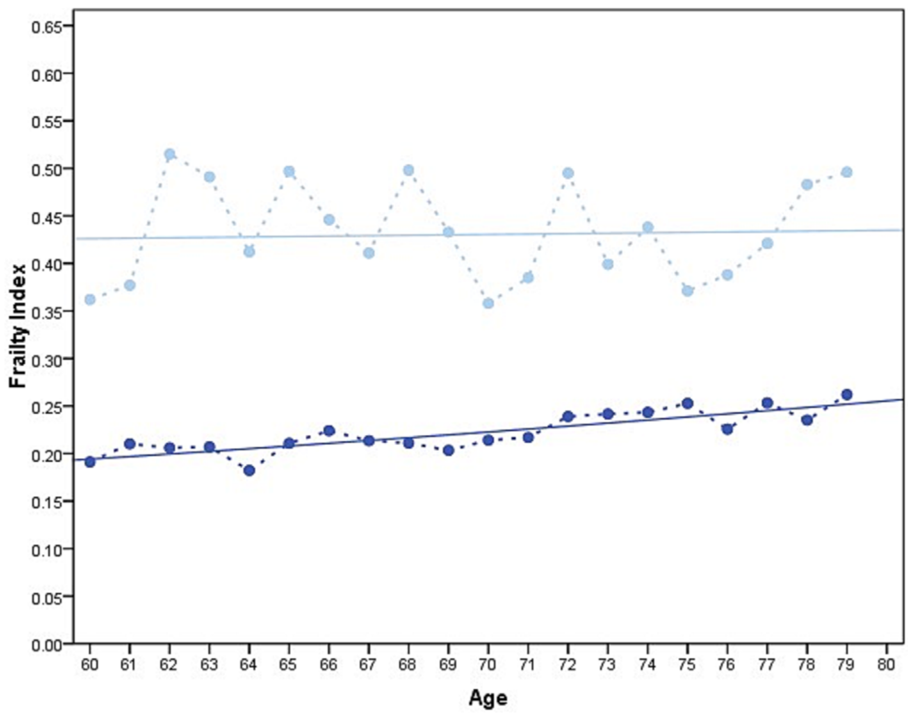

Figure 3 Relationship between the Frailty Index and age. Shown here are the average FI (dark blue) and the 99th of FI (light blue) lines. The average FI-age curve has a 1.4% deficit accumulation per year on a log scale. The 99th of FI slope shows no accumulation of deficits with age.

Discussion

To the best of our knowledge, this is the first study emphasizing the association between sarcopenia and Frailty Index in elderly patients with CKD stage I to IV.

We established a Frailty Index to assess the frailty of these participants. Searle et al.[21] summarized the characteristics of previously published Frailty Indexes: (1) The FI should have a skewed density distribution (histogram) that is well approximated by a gamma distribution; (2) The rate of deficits accumulation (prior estimate is 2.6% per year); (3) The presence of a sub-maximal, age-invariant limit to the FI (prior estimate is 0.60); and (4) Association of the mean value of the FI with mortality. In our study, the FI exhibited a right-skewed distri-

Table 2 Cox regression analysis testing associations between per 1-SD difference in variables and mortality.

Analysis	Variable	HR	95% CI	P
Univariate	Frailty Index	1.07	1.02–1.13	0.001
	Age	1.17	1.07–1.29	0.001
	Male sex	0.14	0.02–1.10	0.062
	CKD 1 (ref)	1		0.653
	CKD 2	1.59	0.29–8.70	0.590
	CKD 3	1.31	0.24–7.18	0.752
	CKD 4	2.88	0.48–17.32	0.247
Multivariate	Frailty Index	1.06	1.00–1.12	0.041
	Age	1.15	1.04–1.27	0.006

The frailty index hazard ratios (HR) were calculated with % levels of the index (i.e. the HR measures a change of 0.01 on the index). Multivariate Cox regression analysis done with age, sex, CKD stages and Frailty Index as covariates.

bution, a rate of deficits accumulation was 1.4% per year, the 99th of FI independent of age was 0.43, and the FI was an independent risk factor of mortality. The rate of deficit accumulation and 99th of FI in China were lower than those in developed countries, which may be related to the younger age of participants (60–79 vs. 72–98) and a survivor effect. In past studies, frailty was defined by a mean FI score from 0.2 to 0.35 based on the difference of FI variables [S17–S20]. In our study, the prevalence of sarcopenia was 30.1% in elderly patients with CKD stage I–IV. As no clinically significant cutoff value for FI levels has been established in this cohort, we cannot determine the prevalence of frailty. As the FI increased, the frailty progressed and the prevalence of sarcopenia in-

Table 3 Univariate logistic regression analysis studying the association between frailty index and selected variables in elderly patients with CKD I–IV

	Median FI tertile		High FI tertile	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.07 (1.04, 1.10)	<0.001	1.10 (1.06, 1.13)	<0.001
Male	1.07 (0.74, 1.54)	0.731	0.91 (0.63, 1.30)	0.602
Sarcopenia	1.40 (0.95, 2.06)	0.09	1.76 (1.21, 2.58)	0.003
CKD stage I	Reference		Reference	
CKD stage II	1.48 (0.87, 2.51)	0.146	2.71 (1.53, 4.81)	<0.001
CKD stage III	1.96 (1.21, 3.18)	0.006	2.92 (1.70, 5.02)	<0.001
CKD stage IV	3.23 (1.82, 5.75)	<0.001	6.53 (3.54, 12.05)	0.001
WHR	1.03 (1.00, 1.06)	0.030	1.04 (1.01, 1.07)	0.005
TSF	1.04 (0.90, 1.20)	0.637	1.02 (0.88, 1.18)	0.815
24 h proteinuria	1.06 (0.99, 1.13)	0.121	1.14 (1.07, 1.22)	<0.001
Cystatin C	1.49 (1.16, 1.91)	0.002	2.05 (1.60, 2.61)	<0.001
Albumin	1.01 (0.99, 1.03)	0.469	0.97 (0.95, 0.99)	<0.001
PTH	1.01 (1.00, 1.01)	0.002	1.01 (1.00, 1.01)	<0.001
Serum phosphorus	1.77 (0.76, 4.12)	0.187	4.03 (1.74, 9.37)	0.001
Serum calcium	1.37 (0.65, 2.88)	0.409	0.54 (0.26, 1.14)	0.105
WBC	1.10 (1.02, 1.18)	0.017	1.09 (1.01, 1.18)	0.027
NE	1.03 (1.02, 1.05)	<0.001	1.03 (1.01, 1.05)	<0.001
LYM	0.96 (0.94, 0.97)	<0.001	0.96 (0.94, 0.98)	<0.001

Low FI tertile as reference group.
CKD, chronic kidney disease; LYM, lymphocyte; PTH, parathyroid hormone; TSF, triceps skinfold thickness; WBC, White blood cell; NE, neutrophils; WHR, waist–hip-ratio.

Table 4 Multivariate logistic regression analysis studying the association between Frailty Index and selected variables in elderly patients with CKD

	Median FI tertile		High FI tertile	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.06 (1.02, 1.10)	0.005	1.08 (1.04, 1.12)	<0.001
Male	0.87 (0.57, 1.31)	0.499	0.73 (0.48, 1.11)	0.142
Sarcopenia	1.43 (0.95, 2.16)	0.086	1.67 (1.10, 2.53)	0.016
CKD stage I	Reference		Reference	
CKD stage II	1.42 (0.79, 2.53)	0.240	2.36 (1.26, 4.42)	0.007
CKD stage III	1.90 (1.00, 3.61)	0.049	2.14 (1.08, 4.23)	0.030
CKD stage IV	3.00 (1.13, 7.94)	0.027	3.17 (1.21, 8.35)	0.019
WHR	1.02 (0.99, 1.05)	0.146	1.03 (1.00, 1.07)	0.030
24 h proteinuria	1.08 (0.98, 1.18)	0.109	1.08 (0.98, 1.17)	0.111
Cystatin C	0.76 (0.50, 1.15)	0.194	1.24 (0.85, 1.81)	0.263
Albumin	1.02 (0.99, 1.04)	0.312	0.97 (0.94, 0.99)	0.012
PTH	1.00 (1.00, 1.01)	0.630	1.00 (1.00, 1.01)	0.512
Serum phosphorus	1.44 (0.54, 3.81)	0.464	1.76 (0.66, 4.70)	0.260
WBC	1.06 (0.97, 1.15)	0.207	1.04 (0.96, 1.13)	0.347
NE	1.00 (0.97, 1.04)	0.855	1.01 (0.97, 1.05)	0.617
LYM	0.97 (0.93, 1.01)	0.136	0.99 (0.94, 1.03)	0.548

Low FI tertile as reference group. Age, sex, CKD stages, sarcopenia, WHR, 24 h proteinuria, serum cystatin C, albumin and PTH, phosphorus WBC, NE% and LYM% as covariates.

Table 5 Subgroup analysis

	Median FI tertile			High FI tertile		
	OR (95% CI)	*P*	*P* for interaction	OR (95% CI)	*P*	*P* for interaction
Total group	1.39 (0.93, 2.08)	0.111		1.60 (1.06, 2.42)	0.025	
Serum albumin			0.014			0.001
<35 g/L(n = 359)	2.28 (1.19, 4.35)	0.013		3.40 (1.80, 6.43)	<0.001	
≥35 g/L (n = 415)	0.94 (0.55, 1.60)	0.811		0.82 (0.46, 1.47)	0.497	

Low FI tertile as reference group. Adjusted for age, sex, CKD stages, WHR, 24 h proteinuria, serum cystatin C, albumin and PTH and phosphorus.

creased. We evaluated FI in tertiles; the Frailty Index of patients was ≥0.25 in high FI tertile, while ≤0.17 in low FI tertile. We can assume that the patients in the high FI tertile were frailer than those in the low FI tertile.

There is considerable overlap between sarcopenia and the physical aspects of frailty [S12]. Most existing studies have analysed the associated factors of frailty and sarcopenia as isolated states, and only a few studies have merged the two conditions into one entity (overlapped frailty and sarcopenia; F&S).[22] Although the association between sarcopenia and frailty has not been fully characterized, sarcopenia and frailty share many commonalities in the underlying mechanisms and pathophysiologic processes, including ageing, immunosenescence, hormonal imbalance, low physical activity, and poor nutritional status and co-morbidities.[23] From a pathophysiologic point of view, F&S may be considered as a condition spanning muscle-specific processes to systemic changes,[24] even though frailty and sarcopenia are different concepts. Our study suggested that sarcopenia was associated factors for frailty defined by FI. There are several speculations here. First, Frailty Index developed by Rockwood[3] defined frailty as an accumulation of deficits across multiple organ systems, including cognition and mood, which overlapped with sarcopenia and was more extensive. Second, various biomarkers for frailty discovered in metabolomics have chiefly focused on amino acids,[25] while metabolites associated with sarcopenia have not been comprehensively profiled and examined. Meng et al.[26] applied a targeted high-performance liquid chromatography–tandem mass spectrometry approach to distinguish elderly patients with frailty from those without frailty by different characteristic metabotypes and found similar characteristic metabotypes between frailty and F&S patients. With sarcopenia or not does not significantly impact the metabolic characteristics of frailty. Third, Nagase et al.[27] found that skeletal muscle atrophy-induced haemopexin accelerates the onset of cognitive impairment in Alzheimer's disease. Frailty correlates with more rapid cognitive decline in Alzheimer's disease, which has been denominated as 'cognitive frailty' [S21–S22]. We indeed think that there is an underlying link between sarcopenia and frailty. An increased risk of frailty in elderly CKD patients with sarcopenia independent of other risk factors.

As reported, human muscle mass decreases at an annual rate of 1–2% after about age 50, while muscle strength declines by 1.5% per year and by 3% after age 60.[28] Sarcopenia and frailty are prevalent in the CKD population. The prevalence of sarcopenia was from 3.9% to 73.5% in CKD patients [S10, S11, S23–S25]. Reduced MAMC and decreased HGS seem to be more common in older (>65 years) than younger maintenance dialysis patients.[29] The prevalence of sarcopenia also increases with ageing in CKD patients without ESRD.[30] Compared with elderly patients with normal renal function, elderly patients with chronic kidney disease, whether dialysis or non-dialysis, have a higher prevalence of frailty (14–73% vs. 13.6%).[31,32] Due to the heterogeneity of the study population and the lacking of unified diagnostic criteria for frailty and sarcopenia, the reported prevalence was quite different. It can be inferred that frailty and sarcopenia of elderly CKD patients are related to renal function or ageing, or both. A similar pathophysiological mechanism of frailty and sarcopenia supports this perspective.[23] In our study, CKD stages and age were associated with frailty, whether in the median or high FI tertile.

In our analysis, comparing patients in high FI tertile with those in low FI tertile, we can assume that sarcopenia was an independent predictor of frailty, and advanced age, higher CKD stages, increased WHR and lower serum level of albumin were other independence risk factors for frailty in elderly patients with CKD stage I–IV. Hong et al.[33] demonstrated that hospitalized older patients with better nutritional status and higher levels of ALB were less likely to develop into frailty. Serum albumin reflects the body's nutritional status. Loss of appetite, nausea, vomiting and other gastrointestinal symptoms induced inadequate food intake, and uraemia induced muscle and fat catabolism, which may lead to malnutrition in elderly patients with CKD.[34] It was reported that protein supplementation, optimally as a leucine-enriched essential amino acid mixture, will improve muscle mass and perhaps decrease frailty[35] [S26, S27]. WHR was a vital index to judge central obesity. Chan et al. [S28] examined the interaction between frailty and obesity in peritoneal dialysis (PD) patients and suggested that frail individuals were more likely to have central obesity but not general obesity. Zaslavsky et al.[36] conducted a longitudinal prospective cohort study with 11 070 frail women aged 65–84 at baseline and found that a WHR of 0.8 or less was associated with lower mortality in frail, elder women. Inoue et al.[37] demonstrated an association between frailty and dipstick proteinuria in elderly CKD patients. Proteinuria was considered the result of kidney damage and seemed to be a major risk factor and pathological stimulus of renal inflammation.[38] It is reasonable that proteinuria is associated with frailty in patients with CKD in univariate logistic regression analysis. Chronic inflammatory state is very common in CKD patients, especially in ESRD, and as the disease progresses more and more severe, and is closely related with sarcopenia, furthermore caused frailty. In our study, high levels of WBC and NE% were associated factors for frailty. There was no statistical significance in WBC and NE% between low FI and median FI patients in multivariate logistic regression analysis. May be advanced age, CKD stage and muscle loss have greater influence on the frailty of elderly CKD patients. Inferences from the subgroup analysis, the correlation between sarcopenia and frailty was affected by serum albumin level. Patients with sarcopenia and low serum albumin ($<$35 g/L) may be at an exceptionally high risk of frailty. The lack of statistically significant associations in the normal serum albumin ($\geq$35 g/L) group may be due to the insufficient number of participants and incident sarcopenia events in each subgroup.

There were some limitations to this study. First, this study is a cross-sectional observational study, and the causal relationship between frailty and associated factors was unclear. We did not know the long-term outcomes of these subjects, and we could not investigate the effects of sarcopenia and frailty on the outcome. Second, this cohort has no accurate cut-off value of frailty according to Frailty Index, as frailty is a complex syndrome. Only the low FI tertile and high FI tertile were compared to make a significant difference in sarcopenia. Patients in median FI tertile, who may be the 'pre-frail' population, had no significant difference in sarcopenia compared with those in low FI tertile. However, patients in median FI tertile were less frail than those in high FI tertile and were easier to be corrected by various interventions. More variables should be found to predict the risk of 'pre-frail' in future studies. Third, body mass index and MoCA-B cut-off values for the Chinese population were used in this study, potentially limiting the generalisability of our Frailty Index.

Conclusions

Sarcopenia and frailty are prevalent in elderly CKD patients even before dialysis. Sarcopenia was independently associated with an increased risk for frailty. Patients with advanced age, sarcopenia, high CKD stage, heavy proteinuria and low serum albumin level should be assessed for frailty. Frailty screening and assessment may provide an opportunity for early detection and intervention to reduce morbidity, prevent adverse health outcomes and make more effective use of medical resources.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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