Original Article

Association of the malnutrition-inflammation score with physical function and functional disability in elderly patients with chronic kidney disease

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Background and Objectives: To describe nutritional status and inflammation of elderly patients with chronic kidney disease and to confirm the association between a Malnutrition-Inflammation Score and physical function and functional disability. **Methods and Study Design:** A total of 221 chronic kidney disease patients (aged ≥60 years) were included. A Malnutrition-Inflammation Score was used to assess malnutrition and inflammation. Physical function was assessed using the SF-12. Functional status was evaluated using basic activities of daily living and instrumental activities of daily living. **Results:** Thirty percent of participants had a Malnutrition-Inflammation Score ≥6, which denoted poor nutritional status. Participants with a Malnutrition-Inflammation Score ≥6 had decreased concentration of hemoglobin, albumin, prealbumin, handgrip strength and walking speed and increased concentration of inflammatory markers, including CRP, IL-6 and fibrinogen. Physical function and physical component summary were lower and basic activities of daily living dependence and instrumental activities of daily living dependence were higher among patients with higher Malnutrition-Inflammation Score than those with a lower Malnutrition-Inflammation Score. The Malnutrition-Inflammation Score was an independent risk factor for physical function and instrumental activities of daily living dependence. **Conclusions:** The elderly chronic kidney disease patients with a high Malnutrition-Inflammation Score had a decreased physical function and an increased risk of functional instrumental activities of daily living dependence.

Key Words: activities of daily living, chronic kidney disease, elderly, malnutrition, physical function

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem.[1] With increased age, the prevalence of CKD increases significantly. The prevalence of CKD is 31.5% for those 65-79 years old and as high as 65.0% in those over 80 years old.[2] Elderly patients with CKD are more likely to suffer mortality than to progress to end-stage renal disease (ESRD) due to complications and comorbidities.[3,4] They also have a high prevalence of geriatric syndromes, including malnutrition and decreased physical capabilities and quality of life.[5-8]

Functional independence is important, and the preservation of functional independence is a key determinant of 'successful aging'. CKD is associated with adverse health outcomes, including lower physical function (PF) and functional disability, which are potently related to all-cause mortality in elderly CKD patients.[9,10] Therefore, it is necessary to identify the risk factors that affect PF and functional independence in CKD patients. An independent, significant association was observed between physical activity (the 30" sit-to-stand test) and the malnutrition-inflammation score (MIS) in patients undergoing peritoneal dialysis.[7] Few studies have been carried out in elderly patients with nondialysis CKD.

The MIS is a widely used method to evaluate nutritional status and inflammation.[11,12] MIS has been related to poor outcomes in CKD patients receiving dialysis or a kidney transplant.[13-15] In progressive CKD patients, the MIS has been validated to assess nutritional status[16] and correlated with high-sensitivity C-reactive protein and IL-6 concentration.[17] In our previous study, we also found that MIS is a practical tool for assessing the nutritional

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status and correlated with body composition measurements in the early stages of CKD patients.[18] Thus, the MIS could be a valuable tool to evaluate the nutrition and inflammation status of nondialysis CKD patients. Whether MIS is associated with PF and functional disability is not well studied in elderly nondialysis CKD patients. The study aims to evaluate the nutritional and inflammation status of elderly nondialysis CKD patients using the MIS and to confirm the association between the MIS and PF and functional disability.

METHODS

Patients and research design

This cross-sectional study was conducted in hospital nephrology departments. A total of 307 patients were assessed for eligibility. A total of 85 patients were excluded because they either did not meet the eligibility criteria or they refused to participate. Finally, a total of 221 nondialysis patients with CKD were included between May 2017 and October 2018. CKD was diagnosed as follows: a history of CKD for more than three months; either the estimated glomerular filtration rate (GFR) was less than 60 mL/min/1.73 m^2, the albumin-to-creatinine ratio (ACR) was more than 30 mg/g or proteinuria was more than 150 mg/24 h. GFR was estimated with the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation. We excluded participants if they (1) were less than 60 years old; (2) were participating in other interventional clinical trials; (3) were diagnosed as having acute kidney injury; (4) were receiving dialysis; (5) had a history of kidney or other organ transplants; (6) had an active malignancy or metastatic cancer within 24 months prior to screening; (7) had HIV infection; (8) were unable to communicate with examiners or unable to complete the study procedure even if assisted; and (9) were unwilling to participate in the study or unable to give informed consent.

The underlying cause of CKD and the history of cardiovascular disease (CVD), hypertension and diabetes mellitus were recorded in detail. The presence of a history of CVD, hypertension and diabetes was defined as previous study.[19] This study was conducted in accordance with the Declaration of Helsinki. It was approved by the Ethics Committee of the Chinese PLA General Hospital (No. S2016-100-02). Written informed consent was given by all patients before their inclusion in the study. The clinical trial registration number was NCT03246204.

Malnutrition-inflammation score

The MIS had 10 components, including patient medical history, physical examination, body mass index (BMI), serum albumin and serum total iron-binding capacity. Each MIS component had four levels of severity, ranging from 0 (normal) to 3 (very severe). The maximum sum of MIS was 30, indicating a severe degree of malnutrition and inflammation.[12] We excluded dialysis vintage from the score because patients receiving dialysis were excluded from our study. All subjective MIS evaluations were finished by the same researcher. We divided patients into three groups based on the tertile of MIS as first tertile (MIS from 0 to 3), second tertile (MIS from 3 to 6), and third tertile (MIS greater than or equal to 6).

Physical function

PF was assessed using the 12-item Short-form Health Survey (SF-12). PF, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health were the eight dimensions of health-related functioning in the SF-12. Subjects were asked to categorize themselves as not limited at all, limited a little, or substantially limited in the performance of each activity. Responses were scored (0-100), and a higher score reflected better function. The physical component summary (PCS) was a normalized score representing overall PF.[20]

Functional status

Functional status was assessed by self-reported measures of basic activities of daily living (BADL) and instrumental activities of daily living (IADL). BADL included bathing, dressing, going to the toilet, transportation, continence and eating.[21] IADL consisted of the ability to use the telephone, shop, prepare food, perform housekeeping, laundry, travel and manage money.[22] We defined functional disability as present if the respondent reported difficulty with one or more of these activities in either the BADL or IADL scales.[23]

Anthropometric evaluation

BMI, mid-arm circumference (MAC) and triceps skinfold thickness (TSF) were obtained within one week of blood sample collection from the patients and were measured three times. The average value was used for analysis. The TSF was measured with a conventional skinfold caliper. MAC was measured on the dominant arm. Mid-arm muscle circumference (MAMC) was derived from TSF and MAC as follows: MAMC = MAC – π * TSF (cm). Walking speed was investigated using the 5-m walking speed test, which was used to measure participants' usual speeds. The handgrip strength test was carried out using a standard handgrip dynamometer (CAMRY, EH101). Participants were asked to stand with their arms extended sideways from the body. After understanding the procedure, they were asked to grip the dynamometer with maximum strength during measurement. Three measurements were carried out for assessment. The maximum grip strength was used for the present study.[24]

Laboratory analysis

Blood samples were collected the morning after an overnight fast. Hemoglobin, C-reactive protein (CRP), IL-6, fibrinogen, and the serum concentration of albumin, prealbumin, creatinine, cystatin C, uric acid, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, parathyroid hormone (PTH), calcium, phosphate and urinary protein excretion were measured by routine methods at the Department of Laboratory Medicine, PLA General Hospital. GFR was estimated with CKD-EPI creatinine equation.

Statistical analyses

The variables were presented as mean ± SD or median (interquartile range) for continuous data and as percentage for categorical data. One-way ANOVA, the Kruskal-Wallis test or χ^2 analysis was used to compare differences,

as appropriate. Spearman's rank correlation was used to determine correlations. PF and PCS were analyzed using linear multivariate regression analysis. The predictors were accepted according to a stepwise algorithm (inclusion criteria: $p<0.05$, exclusion criteria: $p>0.10$). Functional disability was analyzed using logistic regression analysis. The predictors were accepted according to a stepwise algorithm (inclusion criteria: $p<0.05$, exclusion criteria: $p>0.10$). Analyses were performed with IBM SPSS 25.0 software (SPSS Institute, IBM, USA). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 221 (140 men, 81 women) participants were recruited in our study. The median age of the study participants was 65 (62-69) years. The primary kidney diseases were glomerular disease (51.8%), diabetic nephropathy (17.1%), hypertensive nephrosclerosis (4.5%) and other causes (26.6%). The MIS value ranged from 0 to 12, and the median MIS was four. The clinical characteristics of the 221 participants were depicted in Table 1. Participants were stratified by tertiles of MIS as MIS from 0 to 3 (36%), from 3 to 6 (34%) and greater than or equal to 6 (30%). A MIS greater than or equal to 6 denoted poor nutritional status in this study. Compared to patients with a MIS<6, patients with a MIS≥6 had significantly decreased BMI, MAC, handgrip strength and walking speed values, while inflammation markers, including CRP, IL-6 and fibrinogen, had significantly increased in these patients. PF and PCS were lower and BADL dependence and IADL dependence were higher among patients with higher MIS than those with lower MIS.

Correlations between physical function, functional status and MIS

PF and PCS had a negative correlation with MIS. BADL dependence and IADL dependence had a positive correlation with MIS in Spearman's rank correlation (Table 2). The significantly associated variables were used as covariates in multivariate regression analyses. It demonstrated that PF was associated with handgrip strength, cystatin C and MIS after considering potential confounders. PCS was associated with MAC, handgrip strength and walking speed after considering potential confounders (Table 3). The analyses revealed that only walking speed (OR=0.007, 95% CI: 0.001, 0.360, p=0.007) was an independent risk factor for BADL dependence. Walking speed, cystatin C, HDL and MIS were independent risk factors for IADL dependence (Table 4).

DISCUSSION

The findings from the current study suggested that malnutrition was a highly prevalent condition in elderly patients with CKD. Furthermore, we demonstrated that elderly CKD patients with a higher MIS had a lower PF and a higher risk of IADL disability than those with a lower MIS.

Thirty percent of our study population had a MIS greater than or equal to 6. These patients had no significant decrease in GFR, which was different from the results of other studies. Amparo reported that patients with a higher MIS had a lower eGFR expression.[16] The difference between the two studies may be due to the fact that GFR was approximately 50 mL/min/1.73 m^2 in our study, which was much higher than 30 mL/min/1.73 m^2 in Amparo's study. However, the patients in our study had a significant increase in cystatin C, suggesting that CKD may be a cause of an increased MIS.

In this study, patients with a MIS greater than or equal to 6 had lower concentration of albumin and had higher concentration of inflammation markers, including CRP, IL-6 and fibrinogen, suggesting that the MIS may be utilized as a marker of nutrition and inflammatory status in nondialysis CKD patients. Jagadeswaran reported similar findings about the correlation between the MIS and the concentration of high-sensitivity C-reactive protein and IL-6.[17] Rambod also reported that the MIS was superior to the concentration of CRP and IL-6 when evaluating mortality risk in hemodialysis patients.[13]

Elderly CKD patients with a higher MIS had a lower handgrip strength in our study. Fernanda also reported a negative correlation between handgrip strength and MIS in nondialysis CKD patients.[12] Misu reported that malnutrition was related to decreased walking smoothness in community-dwelling elderly adults.[25] In our previous study, we found MIS was negatively correlated with BMI, MAMC, handgrip strength, lean tissue index, fat tissue index, phase angle, hemoglobin and albumin concentrations in the early stages of CKD patients.[18] In this study, we investigated whether the relationship between MIS and nutritional indicators existed in the elderly CKD patients and further investigated the impact on PF, PCS and function status in order to provide evidence for improving quality of life.

We found that patients with a high MIS had decreased PF and PCS. A number of studies addressed PF in ESRD patients or kidney transplant recipients.[26,27] Rambod reported that PF and PCS were decreased with a high MIS.[13] However, few papers have focused on PF in nondialysis patients. In our study, we found that the nutritional indicators as MIS, handgrip strength and walking speed were associated with PF. It may be possible to improve PF by improving the nutritional status.

Increasing the severity of CKD was associated with impaired IADL. Bowling found that IADL decline occurred in 35% of those with CKD and in only 17% of those without CKD. For participants with eGFR less than 45 mL/min/1.73 m^2, the odds of IADL decline were more than threefold greater than those for participants without CKD.[28] The risk factors including anemia, acidosis, hyperphosphatemia, bone and mineral disorders and malnutrition might explain IADL dependence. IADL dependence was independently correlated with an increased risk of malnutrition and had been reported in geriatric outpatients.[29] The association of functional disability with walking speed, cystatin C, HDL and MIS was found in our study. In total, 23.5% of patients had IADL dependence. The improvement of these indicators may help relieve IADL dependence.

There were also several limitations to this study. The analysis used a cross-sectional design, and therefore, longitudinal relationships could not be established. Partici-

Table 1. Clinical characteristics of study subjects stratified by MIS

Characteristics	Total (n=221)	MIS (0-3) (n=79)	MIS (3-6) (n=76)	MIS (≥6) (n=66)	*p*-value
Age (years)	65 (62-69)	65 (62-69)	65 (63-69)	65 (62-70)	0.651
Men (n, %)	140 (63.3)	56 (70.9)	45 (59.2)	39 (59.1)	0.222
CVD (n, %)	70 (31.7)	28 (35.4)	26 (34.2)	16 (24.2)	0.297
Diabetes (n, %)	76 (34.4)	29 (36.7)	29 (38.2)	18 (27.3)	0.342
Hypertension (n, %)	181 (81.9)	70 (88.6)	60 (78.9)	51 (77.3)	0.150
Current smoking (n, %)	99 (44.8)	41 (51.9)	29 (38.2)	29 (43.9)	0.225
Current drinking (n, %)	91 (41.2)	45 (57.0)	25 (32.9)	21(31.8)	0.002
BMI (kg/m^2)	25.4±2.93	26.4±2.46	25.0±2.82	24.6±3.26	<0.001
MAC (cm)	28.4±3.57	29.2±3.3	28.0±3.7	28.0±3.6	0.049
TSF (cm)	1.50 (1.15-1.90)	1.40 (1.10-2.00)	1.50 (1.20-1.80)	1.40 (1.20-1.83)	0.844
MAMC (cm)	23.5±3.78	24.3±3.70	23.0±3.88	23.1±3.67	0.067
Handgrip strength (kg)	25.9±9.88	29.4±9.84	25.2±9.09	22.5±9.61	<0.001
Walking speed(m/s)	0.97±0.25	1.08±0.22	0.92±0.24	0.91±0.26	<0.001
GFR ($mL/min/1.73m^2$)	49.6 (32.2-69.4)	47.1 (33.9-66.2)	55.8 (34.0-75.8)	44.8 (29.1-64.6)	0.094
Creatinine (μmol/L)	118.2 (91.9-168.5)	126.7 (96.4-164.1)	113.1 (83.1-164.0)	128 (100.3-181.5)	0.084
Cystatin C (mg/L)	1.70 (1.32-2.29)	1.62 (1.30-2.14)	1.59 (1.26-2.25)	1.88 (1.53-2.45)	0.005
Urinary protein excretion (g/24h)	2.39 (0.84-4.36)	1.14 (0.24-2.21)	2.87 (1.27-3.94)	4.29 (2.05-5.87)	<0.001
Hemoglobin (g/L)	118.1±20.3	126.2±18.8	116.7±19.5	110±19.4	<0.001
Albumin (g/L)	34.0 (25.9-39.0)	39.5 (37.7-42.5)	31.7 (26.8-35.7)	23.9 (19.6-27.4)	<0.001
Prealbumin (g/L)	28.4±8.87	32.3± 7.62	29.2± 7.34	23.0± 9.25	<0.001
Total cholesterol (mmol/L)	4.71 (3.89-5.85)	4.28 (3.53-4.91)	4.76 (3.91-5.94)	5.35 (4.27-7.85)	<0.001
Triglycerides (mmol/L)	1.76 (1.29-2.60)	1.65 (1.31-2.42)	1.78 (1.18-2.95)	1.91 (1.40-2.59)	0.540
HDL (mmol/L)	1.11 (0.92-1.33)	1.03 (0.85-1.19)	1.16 (0.95-1.34)	1.20 (1.04-1.48)	<0.001
LDL (mmol/L)	2.89 (2.21-3.98)	2.62 (2.02-3.23)	2.93 (2.30-3.97)	3.60 (2.38-5.52)	<0.001
Uric acid(μmol/L)	387.6±98.9	397.3±93.6	387.1±90.5	376.4±113.5	0.449
PTH (pg/mL)	35.4 (25.7-49.0)	39.4 (28.9-57.7)	34.0 (24.5-44.7)	30.7 (22.9-47.2)	0.025
Calcium (mmol/L)	2.10 (2.00-2.22)	2.22 (2.13-2.29)	2.09 (2.01-2.16)	2.00 (1.88-2.08)	<0.001
Phosphate (mmol/L)	1.21± 0.21	1.19± 0.21	1.25±0.20	1.19± 0.21	0.107
CRP (mg/L)	0.10 (0.07-0.20)	0.10 (0.09-0.20)	0.10 (0.06-0.10)	0.10 (0.10-0.53)	0.006
IL-6(pg/mL)	3.71 (2.06-6.82)	3.10 (2.00-5.06)	3.68 (2.09-6.23)	5.71 (2.72-8.93)	0.001
Fibrinogen (g/L)	4.02 (3.33-4.86)	3.56 (3.03-4.18)	4.12 (3.47-4.92)	4.77 (3.77-5.92)	<0.001
PF	69.8±35.7	78.5±33.9	73.7±32.9	54.9±36.8	<0.001
PCS	49.7±9.8	51.7±9.24	50.4±8.69	46.5±10.8	0.004
BADL dependent	6 (2.7%)	0 (0)	2 (2.6)	4 (6.1)	0.040
IADL dependent	52 (23.5%)	11 (13.9)	14 (18.4)	27 (40.9)	<0.001

MIS: Malnutrition-Inflammation Score; CVD: Cardiovascular diseases; BMI: body mass index; MAC: mid-arm circumference; TSF: triceps skinfold thickness; MAMC: Mid-arm Muscle Circumference; GFR: glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PTH: parathyroid hormone; CRP: C-reactive protein; PF: physical function; PCS: physical component summary; BADL: basic activities of daily living; IADL: instrumental activities of daily living.

Table 2. Correlation between physical function, functional status and selected variables

Variables	PF		PCS		BADL dependent		IADL dependent	
	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value
Age (years)	-0.219	0.001	-0.234	<0.001	0.054	0.423	0.229	0.001
Sex	-0.192	0.004	-0.148	0.028	-0.012	0.865	0.132	0.051
BMI (kg/m^2)	0.047	0.491	0.023	0.732	0.066	0.326	-0.002	0.980
MAC (cm)	0.154	0.022	0.170	0.012	-0.020	0.772	-0.062	0.363
TSF (cm)	-0.170	0.012	-0.109	0.105	0.116	0.086	0.066	0.325
MAMC (cm)	0.230	0.001	0.215	0.001	-0.077	0.256	-0.091	0.175
Handgrip strength (kg)	0.438	<0.001	0.398	<0.001	-0.185	0.006	-0.345	<0.001
Walking speed (m/s)	0.337	<0.001	0.352	<0.001	-0.184	0.006	-0.375	<0.001
Cystatin C (mg/L)	-0.245	<0.001	-0.178	0.008	0.112	0.096	0.223	0.001
Albumin (g/L)	0.170	0.011	0.129	0.055	-0.155	0.021	-0.159	0.018
Prealbumin (g/L)	0.175	0.009	0.216	0.001	-0.073	0.280	-0.155	0.021
Hemoglobin (g/L)	0.270	<0.001	0.236	<0.001	-0.045	0.509	-0.196	0.003
Total cholesterol (mmol/L)	-0.053	0.436	0.015	0.828	0.020	0.768	0.148	0.027
Triglycerides (mmol/L)	-0.054	0.421	-0.013	0.847	-0.071	0.293	-0.030	0.656
HDL (mmol/L)	-0.031	0.644	0.046	0.499	0.083	0.217	0.219	0.001
LDL (mmol/L)	-0.028	0.678	-0.002	0.974	0.034	0.612	0.171	0.011
CRP (mg/L)	-0.036	0.594	-0.070	0.297	-0.010	0.887	-0.079	0.244
IL-6 (pg/mL)	-0.073	0.278	-0.102	0.132	0.056	0.407	-0.035	0.606
Fibrinogen (g/L)	-0.044	0.511	-0.038	0.574	-0.026	0.699	-0.003	0.963
MIS	-0.307	<0.001	-0.260	<0.001	0.144	0.032	0.299	<0.001

PF: physical function; PCS: physical component summary; BADL: basic activities of daily living; IADL: instrumental activities of daily living; BMI: body mass index; MAC: mid-arm circumference; TSF: triceps skinfold thickness; MAMC: Mid-arm Muscle Circumference; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein; MIS: Malnutrition-Inflammation Score.

Table 3. Multiple linear regression analyses between physical function and selected variables

Variables	PF		PCS	
	B	*p*-value	B	*p*-value
Age	-0.108	0.079	-0.104	0.107
MAC	0.079	0.186	0.127	0.040
Handgrip strength	0.350	<0.001	0.253	0.001
Walking speed	0.129	0.068	0.221	0.003
Cystatin C	-0.158	0.009	-0.102	0.099
MIS	-0.174	0.006	-0.121	0.062

PF: physical function; PCS: physical component summary; MAC: mid-arm circumference; MIS: Malnutrition-Inflammation Score
The predictors were accepted according to a stepwise algorithm (inclusion criteria: $p<0.05$: exclusion criteria: $p>0.10$).

Table 4. Logistic regression analyses between IADL dependent and selected variables

Variables	IADL	
	OR (95% CI)	*p*-value
Walking speed	0.034 (0.007, 0.165)	<0.001
Cystatin C	1.964 (1.201, 3.211)	0.007
HDL	2.938 (1.084, 7.967)	0.034
MIS	1.199 (1.051, 1.367)	0.007

IADL: instrumental activities of daily living; HDL: high-density lipoprotein; MIS: Malnutrition-Inflammation Score.
The predictors were accepted according to a stepwise algorithm (inclusion criteria: $p<0.05$, exclusion criteria: $p>0.10$).

pants from a single center were recruited, and a larger sample size was needed to confirm the conclusion from the study. The association of MIS with physical function and functional disability was found in elderly CKD patients in this study while we did not comparative with a non-CKD group. Nutrition and caloric intake were not related in the study. A potential source of bias existed because of unwillingness to participate as an exclusion criterion.

Conclusion

The results of our study suggested that malnutrition in elderly CKD patients was high. Elderly CKD patients with a high MIS had a decreased physical function and an increased risk of IADL disability. Improvement on the nutrition status may help patients in physical function and give them further benefits.

AUTHOR DISCLOSURES

The authors have no conflicts of interest to disclose.

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