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Association of frailty with nutritional parameters in patients with chronic kidney disease

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ABSTRACT

Objectives: Frailty is a significant clinical syndrome characterized by greater susceptibility to stressors due to the dysfunction of multiple organ systems, which increases in prevalence with age. This study was performed to investigate relations between frailty and nutritional parameters in patients with chronic kidney disease (CKD).

Methods: This cross-sectional study involved 100 CKD patients aged 50 years or older. Frailty was assessed using the Edmonton Frailty Scale (EFS) and Fried's Frailty Scale (FFS). The patients nutritional status was assessed using the Mini Nutritional Assessment (MNA) and the routine laboratory tests.

Results: The study included 100 patients, consisting of 41 females and 59 males. The mean age of the participants was 65.3±9.3 years. The median glomerular filtration rate (GFR) of the patients was 23 mL/min/1.73 m2) (min: 3-max: 65). According to the MNA, 15 patients had normal nutritional status, 63 were at risk of malnutrition, and 22 were malnourished. According to the EFS score, four patients were categorized as not frail, 11 as vulnerable, 25 with mild frailty, 21 with moderate frailty, and 39 with severe frailty. According to the FFS score, six patients were non-frail, 30 were classified as pre-frail, and 64 were considered frail.

Conclusions: Frailty and malnutrition in patients with CKD were independently related to all other factors examined in this study. Screening for malnutrition at the early stages in patients with CKD and the appropriate treatment may prevent the development of frailty.

Keywords: Chronic kidney disease, frailty, malnutrition

Frailty is a significant clinical syndrome in elderly populations characterized by an increased vulnerability to stressors due to dysfunction in multiple organ systems. Its prevalence increases with age due to diminishing physiological reserves and subclinical organ dysfunction [1]. Additionally, individuals with chronic diseases appear to be predisposed to frailty [2].

Nutritional status is a compound concept involving food intake, body composition, and functional capacity. Nutritional assessment to identify malnutrition is based on anthropometric measurements and laboratory tests [3]. Renal dysfunction represents a substantial risk factor for mortality in elderly patients. A lower-than-expected glomerular filtration rate (GFR) for a person's age is linked to an increased risk of death

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[4, 5]. The risk of developing sarcopenia rises as renal function declines in individuals with CKD. The major causes of sarcopenia are considered to be type II muscle atrophy resulting from changes in protein metabolism and a decline in mitochondrial function [6]. Muscle mass loss in CKD patients is associated with reduced grip strength and slow walking speed, leading to poor muscle mass [7].

Although there have been many studies on frailty in CKD, there have been few studies regarding the relationship between frailty and nutritional status in CKD. Therefore, this study was conducted to examine the association between frailty and nutritional parameters in patients with CKD.

METHODS

Study Design

A total of 100 patients diagnosed with CKD, who had no active infection or malignancy, and were over 50 years of age, presenting to Selçuk University School of Medicine Nephrology Outpatient Clinic, Konya, Turkey, between October 2015 and July 2016 were included in the cross-sectional study. The study protocol was approved by the local ethics committee (approval number: 2015/208, Date: 23.06.2015). All of the patients had no history of chronic alcohol consumption. We recorded patients' demographic characteristics, duration of illness, medications taken, and whether they lived alone, with family, or with a partner.

The diagnosis of CKD was established following the diagnostic criteria outlined: Improving Global Outcomes (KDIGO) guidelines. CKD stage was determined according to the KDIGO guidelines [8].

Evaluation of Nutritional Status

The Mini-Nutritional Assessment (MNA) was employed to assess the nutritional status [9]. Patients were divided into three groups according to their MNA scores: ≤ 17 points, malnutrition; 17–23.5 points, risk of malnutrition; ≥ 24 points, normal nutritional status. Muscle power was assessed by testing hand grip strength using a hand dynamometer (JIMCO rehab®). Measurements were obtained on both sides with the elbow flexed at 90°, the upper arm aligned with the patient's side, and recorded as the average of three measurements. Average measurements below the expected values according to the patient's BMI indicated low muscle strength. Anthropometric measurements (height, weight, BMI, mid-arm circumference [MAC], hip circumference, calf circumference, and subcutaneous fat thickness measurements) were obtained during outpatient visits.

Evaluation of Frailty

Frailty was evaluated using both the Edmonton Frailty Scale (EFS) and Fried's Frailty Scale (FFS) [10, 11]. The EFS contains nine components, each scored from 0 to 17. Patients were categorized based on their EFS score as follows: 0-4, not frail (subgroup E1); 6-7, vulnerable (subgroup E2); 8-9, mild frailty (subgroup E3); 10-11, moderate frailty (subgroup E4); 12-17, severe frailty (subgroup E5). The FFS contains five components: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. Patients fulfilling none of these criteria were classified as not frail (subgroup F1), those fulfilling 1-2 criteria as pre-frail (subgroup F2), and those fulfilling ≥ 3 criteria as frail (subgroup F3). Routine laboratory parameters were recorded.

Statistical Analysis

Variables (age, sex, weight, and BMI) are presented as the mean ± standard deviation (SD), range (min–max), or median and percentage (%) as appropriate. The $\chi 2$ test was employed to compare categorical data across different groups. The Kruskal–Wallis test was utilized for the analysis of laboratory parameters, and the Mann–Whitney U test was employed for subgroup analysis due to the non-normal distribution of patients in accordance with the frailty scale groups. Multivariable linear regression analysis (independent variables: age, sex, diabetes mellitus, hemoglobin, albumin, MNA, and GFR) was used to determine factors independently associated with EFS and FFS scores.

RESULTS

The study included 100 patients aged 50 years or older with CKD. This group consisted of 41 females and 59 males, averaging 65.3±9.3 years. The demographic information and anthropometric measurements of the

patients are presented in Table 1. The median GFR of the patients was 23 mL/min/1.73 m2 (min: 3-max: 65), and the median follow-up duration for CKD was 44 months (min: 3-max: 300 months).The patients had a mean BMI of 29.4±6.3 kg/m2. Seventy-one patients (71%) were not on dialysis, 21 (21%) were on hemodialysis, and 8 (8%) were on peritoneal dialysis. The median follow-up duration for patients undergoing hemodialysis was 36 months (min: 12-max: 180), while for peritoneal dialysis patients, the median follow-up period was 30.5 months (min: 12-max: 48). The distribution patients according to CKD stage was as follows; stage 2 (n = 4), stage 3 (n = 39), stage 4 (n = 19), and stage 5 (n = 38) CKD.

Table 1. Demographic characteristics and anthropometric measurements of patients with chronic kidney disease

Demographic characteristics of patients	n=100
Age (year)	65.3±9.3
Height (cm)	162.6±7.8
Weight (kg)	76.9±15.9
Body mass index (kg/m^2)	29.4±6.3
Anthropometric measurements	
Middle arm circumference (cm)	24.3±3.8
Calf circumference (cm)	32.5±4.6
Hip circumference (cm)	103.5±11.9
Waist circumference (cm)	95.7±12.6
Biceps skin fold thickness (mm)	1.35 (0.7-9.3)
Triceps skin fold thickness (mm)	2 (1-14.2)
Muscle strength (kg)	20 (7-45)
Walking Speed (sec)	11 (6-18)
Comorbidities, n (%)	
Cerebrovascular events	16 (16)
Hypertension	88 (88)
Coronary artery disease	50 (50)
Hyperlipidemia	36 (36)
Chronic obstructive pulmonary disease	28 (28)
Chronic heart failure	27 (27)
Diabetes mellitus	49 (49)

According to EFS score, 4 patients were not frail, 11 were vulnerable, 25 had mild frailty, 21 had moderate frailty, and 39 had severe frailty. According to FFS score, 6 were not frail, 30 were pre-frail, and 64 were frail. According to the MNA scores, 15 patients had normal nutritional status, 63 were at risk of malnutrition, and 22 were malnourished. The comparison of laboratory test results and anthropometric measurements of the patients with different levels of frailty based on EFS results is shown in Table 2. In the whole study population, serum albumin (P=0.003), total cholesterol (P=0.019), LDL (P = 0.025), iron (P=0.008), biceps skinfold thickness (P=0.008), and triceps skinfold thickness (P<0.0001) were significantly different (Table 2).

Laboratory parameters and anthropometric measurements were compared between patients classified according to FFS score (Table 3). In the whole study group, serum creatinie (P = 0.032), serum albumin (P=0.034), vitamin D (P=0.018), GFR (P=0.012), MAC (P=0.009), biceps skinfold thickness (P=0.006), and triceps skinfold thickness (P=0.011) were significantly different (Table 3).

When patients with CKD were grouped based on EFS, the MNA scores significantly differed in the whole study population (P trend = 0.005). As a result of this evaluation, 15 (15%) of the patients were in normal nutritional status, 63 (63%) were at risk of malnutrition, and 22 (22%) were malnourished. In subgroup analysis, MNA scores showed significant differences between the not frail and moderately frail patients (P=0.035), not frail and severely frail patients (P=0.009), vulnerable and severely frail patients (P=0.010), and mildly frail and severely frail patients (P=0.016) (Fig. 1).

Similarly, when patients with CKD were grouped based on FFS, the MNA scores were significantly in in the whole study population (P trend =0.0001). In subgroup analysis, MNA scores showed significant variance between not frail and frailty (P<0.001) and pre-frailty and frailty (P<0.001) (Fig. 2).

In a multivariable linear regression analysis, several factors were identified as independently associated with the EFS and FFS scores. For the EFS score, these factors included age (beta = 0.342, 95% CI = 0.021 - 0.066, P<0.0001), MNA (beta = 0.334, 95% CI: 0.309 - 1.000, P<0.0001), and serum albumin level

Table 2. Laboratory results and anthropometric measurements of patients with chronic kidney disease based on Edmonton Frailty Scale subgroups

Parameters	E1	E2	E3	E4	E5	P value
Age (year)	63.0±5.2	62.6±7.5	60.4±8.2	65.6±9.3	69.2±9.4	**0.008**
Gender (M/F) (n)	3/1	8/3	16/9	12/9	20/19	0.639
Urea (mg/dL)	75.1±51.3	73.2±54.8	91.6±36.4	94.8±45.6	92.3±33.0	0.139
Creatinine (mg/dL)	1.4 (1.4-6.7)	1.4 (1.2-11.8)	3.1 (1.2-10.8)	3 (1.2-11.7)	2.7 (1.1-13.6)	0.136
Albumin (g/dL)	4.2±0.2	4.2±0.4	3.6±0.6	3.9±0.5	3.7±0.4	**0.003**
Total cholesterol (mg/dL)	156±42.1	222±50.6	190±54.2	168±26.7	187.4±36.2	**0.019**
LDL cholesterol (mg/dL)	92.5±35.6	144.9±38	114±50.3	103±25.4	117.5±30.2	**0.025**
HDL cholesterol (mg/dL)	29.0±3.1	36.3±8.6	40.8±13.5	34.2±9.2	39.8±13.0	0.147
Iron (uq/dL)	66.5 (51-300)	73 (21-120)	51 (21-124)	73 (35-212)	51 (13-143)	**0.008**
Ferritin (ng/mL)	152.2 (11-490)	90 (8.5-427)	208 (23-2000)	248 (11-1444)	237 (13-2000)	0.269
Vitamin D (ng/mL)	15.4±9.7	19.3±9.6	18.1±10.1	15.2±10.4	13.3±7.7	0.240
GFR (mL/dk/1.73 m^2)	47.5 (7-51)	38 (3-52)	13 (5-64)	17 (5-48)	19 (4-65)	0.091
Middle arm circumference (cm)	27±2.4	26.4±3.6	24.1±3.4	24.1±3.7	23.6±4	0.114
Calf circumference (cm)	34.7±3.7	34.4±3.2	32.4±5.5	32.2±4.1	32±4.6	0.350
Hip circumference (cm)	109±11.1	106±5.6	99±11.9	104±12.7	104±12.5	0.075
Waist circumference (cm)	97±12.1	103±6.5	91±13.2	96±12.3	95±13.2	0.084
Biceps skin fold thickness (mm)	2.5 (1.9-2.8)	2.1 (1.2-2.5)	1.4 (0.7-8)	1.2 (0.8-2.4)	1.2 (0.8-9.3)	**0.008**
Triceps skin fold thickness (mm)	3.8 (2.2-5.4)	2,3 (1.4-3.6)	2 (1-9)	1.8 (1.1-3.1)	2 (1.1-14.2)	**0.047**
Muscle strength (kg)	37 (25-45)	30 (13-38)	22 (10-40)	20 (12-35)	18 (7-30)	**<0.0001**

Data are shown as mean±standard deviation or median (minimum-maximum or number. Patients were categorized based on their EFS score as follows: 0-4, not frail (subgroup E1); 6-7, vulnerable (subgroup E2); 8-9, mild frailty (subgroup E3); 10-11, moderate frailty (subgroup E4); 12-17, severe frailty (subgroup E5). LDL=Low-Density Lipoprotein, HDL=High-Density Lipoprotein, GFR=Glomerular Filtration Rate

(beta: −0.208, 95% CI: −0.885 - −0.022) (P=0.042). For the FFS score, the factors included age (beta: 0.232, 95% CI: 0.004 - 0.026, P=0.007), MNA (beta: 0.371, 95% CI: 0.202 - 0.538, P=0.016), and GFR (beta: −0.244, 95% CI: −0.016 - −0.002, P=0.008).

DISCUSSION

The term "frail" typically encompasses unexplained weight loss, muscle weakness, reduced walking speed, and diminished physical activity. Medical, socioeconomic, and psychiatric problems in CKD contribute to the development of frailty. Frailty is a multisystemic condition that causes reduced physiological capacity. In patients not undergoing renal replacement therapy, a decrease in GFR of less than 50 mL/min/1.73 m2 has been shown to reduce oral intake in patients with poor renal function, leading to poor nutritional status, and malnutrition [1, 3, 12].

The frailty seen in end-stage renal disease (ESRD) patients is independent of age, and most patients show protein energy malnutrition. However, sarcopenia (determined by measurement of the MAC) and dynapenia (determined by measurement of hand grip strength) seen in malnutrition has a higher prevalence in older than in young patients with CKD [1, 13].

In the current study, there were conflicting findings regarding the relations of EFS and FFS scores with sex and age. Here, EFS and FFS scores showed no significant relationship with sex (P=0.639 and P=0.109), but were significantly related to age

Table 3. Laboratory results and anthropometric measurements of patients with chronic kidney disease based on Fried Frailty Scale subgroups

Parameters	F1	F2	F3	P value
Age (year)	62.5±5.0	61.8±9.0	67.2±9.3	**0.028**
Gender (M/F) (n)	5/1	21/9	33/31	0.109
Urea (mg/dL)	66.4±43.4	73.1±35.2	99.9±38.6	**<0.0001**
Creatinine (mg/dL)	1.4 (1.2-6.7)	1.9 (1.1-11.8)	3.1 (1.2-13.6)	**0.032**
Albumin (g/dL)	4.3±0.3	3.8±0.6	3.7±0.4	**0.034**
Total cholesterol (mg/dL)	173±49.8	197.5±57.5	182.7±34.9	0.504
LDL cholesterol (mg/dL)	110.6±46.3	122.4±50.9	112.8±28.8	0.818
HDL cholesterol (mg/dL)	32±7	40.6±12.8	37.5±11.8	0.323
Iron (uq/dL)	72.5 (33-300)	60 (21-124)	54 (13-212)	0.426
Ferritin (ng/mL)	48.7 (11-490)	158.5 (23-2000)	254 (8.5-2000)	0.142
Vitamin D (ng/mL)	17.2±11.7	19.8±10.2	13.6±8.1	**0.018**
GFR (mL/dk/1.73 m^2)	38 (7-51)	35 (3-65)	16.5 (4-58)	**0.012**
Middle arm circumference (cm)	27.3±2.5	25.4±4.2	23.4±3.5	**0.009**
Calf circumference (cm)	33±2.8	34±5.8	31.8±4	0.163
Hip circumference (cm)	104.6±8.9	105±14.3	102.7±10.9	0.798
Waist circumference (cm)	97.1±10.2	97.8±13.7	94.6±12.4	0.306
Biceps skin fold thickness (mm)	2.1 (1.5-2.7)	1.6 (0.7-5.4)	1.2 (0.7-9.3)	**0.006**
Triceps skin fold thickness (mm)	2.5 (2-5.4)	2.2 (1-6.2)	1.8 (1.1-14.2)	**0.011**

Data are shown as mean±standard deviation or median (minimum-maximum or number. Patients fulfilling none of these criteria were classified as not frail (subgroup F1), those fulfilling 1-2 criteria as pre-frail (subgroup F2), and those fulfilling ≥3 criteria as frail (subgroup F3). LDL=Low-Density Lipoprotein, HDL=High-Density Lipoprotein, GFR=Glomerular Filtration Rate

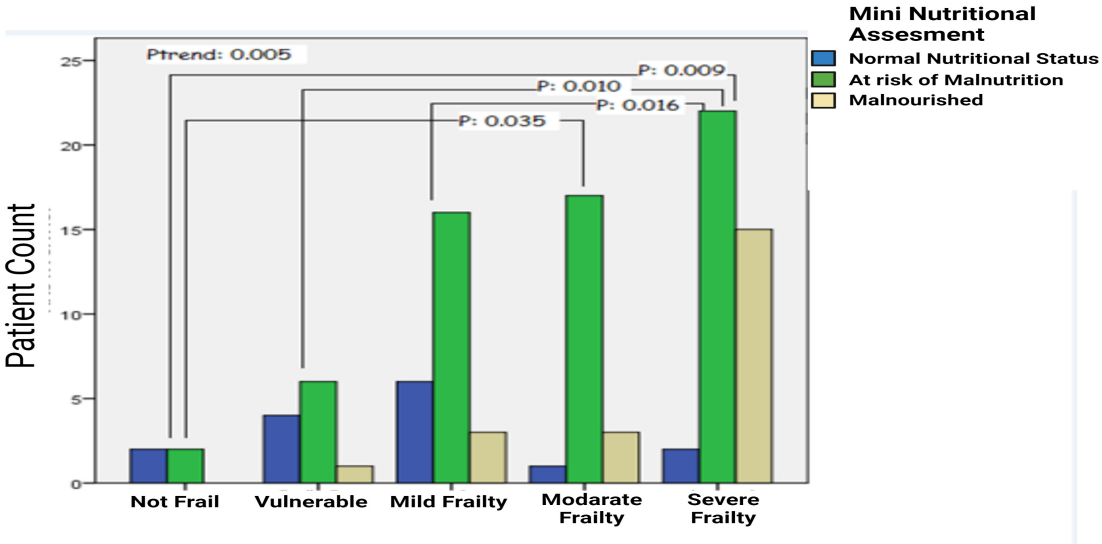

Fig. 1. Comparison of mini-nutritional assessment results of Edmonton Fragility Scale subgroup.

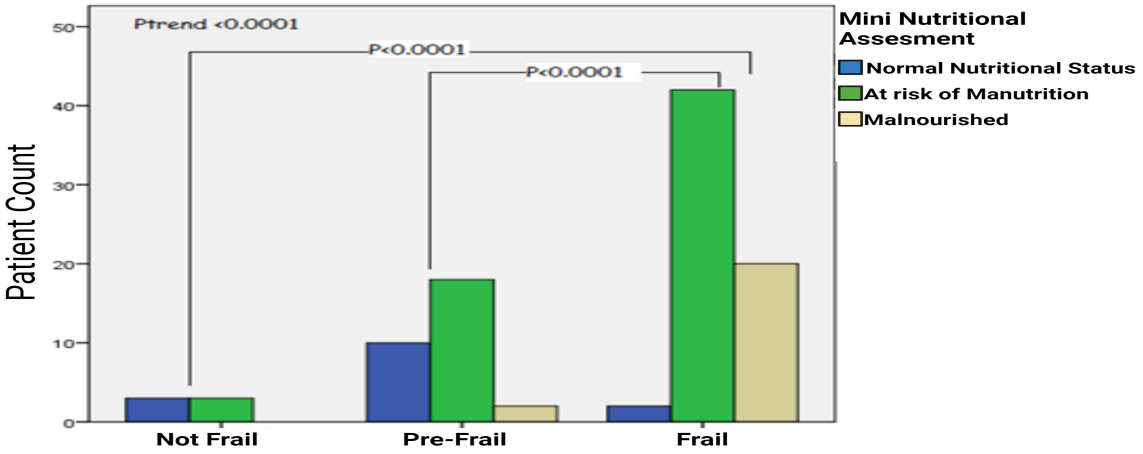

Fig. 2. Comparison of mini-nutritional assessment results of Fried's Fragility Scale subgroup.

(P=0.008 and P=0.028, respectively). Subgroup analyses showed that these differences were mainly between patients with severe frailty and those without frailty.

The actual incidence of frailty was shown to be higher than that detected using clinical assessment indexes, which is thought to be due to differences in the definitions of frailty [14]. In systematice review, Collard *et al*. [15] reported significant relationships between both increasing age and female sex with frailty in community-residing adults aged 65 and above. The same study showed that the prevalence of frailty differs among countries due to the different scales used for evaluation.

A strong relationship was found between CKD and frailty. The incidence of frailty was reported to increase according to increasing CKD stage [1, 16, 17]. Consistent with the literature, GFR was found to be associated with both EFS and FFS independently of other factors in the present study. In patients with CKD receiving hemodialysis, malnutrition is seen at high rates of up to 22.2 %, and malnutrition is strongly related to both morbidity and mortality [18]. Malnutrition is seen in 23%-76% of patients on hemodialysis and 15%–50% of those on peritoneal dialysis [19]. In the present study, MNA scores showed significant differences according to EFS and FFS in patients with CKD (Ptrend=0.005, Ptrend=0.001); the rate of malnutrition increased with increasing frailty.

Low serum albumin levels are a good indicator of malnutrition in HD patient groups [20]. Research indicates a reverse correlation between serum albumin levels and mortality and morbidity, both in the community and in patients admitted to the hospital [21]. Chia-ter Chao *et al*. [22] identified a negative correlation between frailty and serum albumin levels in HD patients. Similarly, in our study, serum albumin levels were notably reduced in CKD patients with frailty compared to those without frailty, as evaluated through EFS and FFS. (P=0.003 and P=0.034).

Reduced vitamin D levels are correlated with fractures, sarcopenia, disability, and frailty. In the InCHIANTI study, low vitamin D level was accepted as a predictor of frailty [23]. Similarly, Puts *et al*. [24] reported a highly significant relationship between low 25-hydroxyvitamin D levels and the presence of frailty. In the present study, vitamin D levels were similar between the groups with and without frailty as assessed by EFS (P=0.240). However, a significant difference was observed between the groups regarding frailty when assessed using FFS (P=0.018). This difference may have been due to implementation of different physical performance criteria in these scales.
Matos *et al*. [25] examined the correlation between the MNA and hand grip test, and reported that hand grip strength could be used as a significant predictor of malnutrition. In the current investigation, it was also observed that hand grip strength decreased as the severity of frailty, as assessed by EFS, increased (P<0.0001). In the present study, MAC measurement was similar within EFS groups (P=0.114), while MAC was significantly different between different FFS

groups (P=0.009). These observations indicated that MAC measurement alone could not be used as an indicator of frailty.

Skinfold thickness measurements offer dependable data for estimating body fat. About 50% of body fat is subcutaneous, making skinfold thickness a directly measurable indicator using a well-calibrated caliper [26]. Triceps skinfold thickness is frequently employed due to its straightforward application. Triceps skinfold thickness was found to be the most accurate parameter for calculating total body fat percentage in a study using dual-energy X-ray scanning as a reference, in a population of hemodialysis patients [27]. In our study, biceps skinfold thickness and triceps skinfold thickness measurements showed a statistically significant difference in the whole study group for both EFS and FFS. Thus, both biceps and triceps skinfold thicknesses can be implemented to assess malnutrition in frail patients with CKD.

Malnutrition is a prevalent condition among individuals with CKD. Malnutrition increases frailty and adversely affects rates of morbidity and mortality if not diagnosed and treated. Although both frailty and malnutrition are common in patients with CKD, the associations of frailty with nutritional parameters are not fully understood. A few studies are available on the relationship between frailty and nutritional parameters in CKD patients. In the present study, frailty was shown to be correlated with a number of nutritional parameters (albumin, LDL, vitamin D, hemoglobin, biceps skin fold thickness, triceps skin fold thickness, muscle strength, MAC) in patients with CKD over 50 years old. In this study, we showed that malnutrition was a strong indicator of frailty in patients with CKD. Similarly, age and GFR were independently linked to frailty in our population of patients with CKD.

CONCLUSION

Malnutrition is independently related to frailty among individuals with CKD. Screening for malnutrition and appropriate treatment beginning from the early stages of CKD is warranted for prevention of the development of frailty.

Authors' Contribution

Study Conception: RE, REA; Study Design: RE, REA; Supervision: REA; Funding: REA, MZK; Materials: RE; Data Collection and/or Processing: RE; Statistical Analysis and/or Data Interpretation: REA, MZK; Literature Review: RE, MZK; Manuscript Preparation: RE, MZK and Critical Review: REA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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