RESEARCH

FRAILTY AND RELATED FACTORS IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Introduction: Chronic kidney disease and frailty are two crucial clinical conditions increasing in prevalence globally. Both lead to severe complications that increase mortality and morbidity in patients. Conditions that may potentiate frailty in chronic kidney disease patients may complicate the follow-up of chronic disease and complicate long-term survival in this patient group. In this study, we aimed to evaluate frailty and related factors in chronic kidney disease patients over 65 years of age who were on dialysis and who were not.

Materials and Methods: This cross-sectional study was carried out in geriatric chronic kidney disease patients followed in nephrology outpatient clinics or undergoing routine hemodialysis. Frailty was assessed using a scoring scale. Laboratory findings and their relationship with demographic and epidemiological data were investigated.

Results: One hundred eighty-eight patients aged 65 and over were included in our study. Of the patients, 92 were female, and 96 were male. The mean age was 72.86 years. We found frailty in 82 patients (43.6%). Female gender, over 75 years old, under dialysis treatment, low-income status, and low education level were parameters significantly associated with frailty. In the regression analysis, we found that economic status and dialysis were variables that independently affected frailty in chronic kidney disease patients.

Conclusions: In our study, the frequency of frailty was found to be high. Practical management and early assessment of frailty seem rational with the basic nephrological approach in patients with chronic kidney disease. Considering the high mortality rate among frail patients, we think these patients should be followed up more closely.

Keywords: Frailty; Aged; Renal Insufficiency, Chronic.

INTRODUCTION

With the increase in the elderly population globally and in Turkey, some geriatric syndromes with low awareness in previous decades have become more common. One of these geriatric syndromes is frailty (1).

Frailty is a dynamic entity with a decrease in physical, mental, and social life potentials advancing age and subsequent clinical, cognitive, and psychological negative consequences (2). It is a heterogeneous process that must be evaluated effectively in clinical practice, mainly because it causes an increase in morbidity and mortality in geriatric patients. Frail elderly patients have low physical performance abilities and a high probability of experiencing general health problems (3).

Chronic kidney disease (CKD) is a progressive, chronic clinical entity with various serious complications, an independent risk factor for cardiovascular disease, and a serious public health problem. Both morbidity and mortality are high among CKD patients, the incidence of which is increasing daily all over the world, and this creates a serious cost burden for health systems (4). However, many studies have shown that frailty increases in patients with CKD. It may be over 60% of patients receiving hemodialysis (HD) (2). Also, it was reported that frail patients had less planned dialysis initiation than a non-frail group (5).

As renal functions worsen, malnutrition and sarcopenia tend to increase in CKD patients due to uremic nausea and vomiting, insufficient oral intake due to gustatory changes, polypharmacy, concomitant chronic diseases, and strict diet practices. This challenging setting provides suitable grounds for frailty in patients (6). However, it has also been suggested that some non-pharmacological approaches may positively affect frail patients receiving hemodialysis. For example, some approaches as interventions to correct nutritional deficits and weight loss can help reduce the frailty level of patients. Therefore, early diagnosis of frailty is crucial in treatment management in CKD patients (2, 7).

It has been shown that mortality increases in frail patients in the pre-dialysis group and patients undergoing dialysis (5, 8). As the severity of the disease increases in CKD patients, the frequency of frailty also increases (6). In this study, we examined the frequency of frailty and related parameters in patients who were followed up for chronic kidney injury.

MATERIALS AND METHODS

Study design and participants

In this cross-sectional study, the G-Power program calculated the sample size at a 90% confidence level before the data collection phase. In this study, we planned to investigate CKD patients' frailty status risk factors. For this, a chi-square analysis was conducted. The study's effect size was 0.30; by taking the alpha value of 0.05 and the theoretical power of 0.90, the minimum number of samples was determined to be 183.

We evaluated 188 patients with CKD (stage II-VD), aged ≥65, who were followed up between 02/09/2018 and 04/01/2020 at the nephrology outpatient clinics at Manisa Celal Bayar University Hospital and Bakırçay University Çiğli Regional Education and Research Hospital. Patients with active solid organ or hematological malignancy, dementia or Alzheimer's disease, a history of cerebrovascular disease, physical limitations, hearing or speech difficulties, acute kidney injury, and hemodynamically unstable patients were excluded from the study.

Data collection tools

A sociodemographic data survey and the Edmonton Frail Scale (EFS) were administered to each patient.

Sociodemographic data survey

Demographic and epidemiological (age, gender, duration of disease) findings, basic biochemical tests, hemograms, sub-parameters, and comorbid conditions (diabetes, hypertension, chronic lung disease, and cardiovascular disease) were examined.

The Edmonton Frail Scale

The EFS is an assessment tool that can be used alone or in combination with other scales and can be easily applied to hospitalized and outpatients in assessing frailty, as defined by Rolfson et al. and validated in the Turkish population (9, 10). Those with a score of 0–4 were evaluated as non-frail, 5–6 apparently vulnerable, 7–8 as mildly frail, 9–10 as moderately frail, and 11 and above severely frail. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical analysis

In the statistical analysis, when descriptive statistics were provided for normal distribution conditions, Student's t-tests and ANOVA were employed to compare the two independent groups in continuous data. The data obtained from the study were evaluated using SPSS 15.0. If the normal distribution conditions were not met, the Mann-Whitney U and Kruskal-Wallis tests were applied.

Ethical procedure

Permission was obtained from the local University Faculty of Medicine Health Sciences Ethics Committee (Manisa Celal Bayar University) with date and no. 30.05.2018/20.478.486. Each patient was informed about inclusion in the study, and their consent was obtained.

RESULTS

One hundred eighty-eight patients were included in the study. Of the patients, 96 were male. The patients who were aged between 65 and 99 years were included in the study. The mean height was 164.96 cm and weight 75.5 kg. Patients had a history of hypertension in 72.9%, chronic lung disease in 12.8%, diabetes mellitus in 47.3%, and cardiovascular disease in 41%. The patients living with their spouse comprised 53.2% of the total, while 21.3% were living with their spouse or children, 19.7% were living alone, and 5.9% were living in a nursing home (Table 1).

According to the CKD stages, the distribution was as follows: stage II 19 patients (10.1%), stage III 87 (46.3%), stage IV 46 (24.5%), and stage V 36 (19.1%). The mean hemoglobin level of the patients was 11.96 ± 1.93 g/dl (min. 7.1–max. 18 g/dl). Hemoglobin was found to be 12 g/dl > in 95 (50.5%) patients.

We found frailty in 82 (43.6%) patients when we combined frail patients according to the EFS with a holistic evaluation.

Among the frail patients, the female gender was significantly higher (64.6% vs 35.4%, $p = 0.001$). Women were more frail than men (7.11 ± 2.92 vs 5.3 ± 2.87, $p = 0.001$). However, this significance was unrelated to CKD staging by gender. Frailty was higher in patients over 75 years of age than in patients 75 years and younger ($p = 0.012$).

In the evaluation made according to the education level of the patients, it was observed that there was a significant difference between the groups in terms of frailty ($p = 0.001$). It was determined that primary school-educated and literate patients were more frail than other education levels ($p = 0.001$).

Table 1. Distribution of patient characteristics

Features		
	S/Ort.	% (or SS*)
Gender		
Female	92	48.9
Male	96	51.1
Age		
Mean	72.86*	6.41*
65-74 years	122	64.9
75-84 years	55	29.3
≥ 85 years	11	5.9
Education		
Primary school and Literate	149	79.3
Middle and High School	26	13.8
University	13	6.9
Marital status		
Married	128	68.1
Not married (widowed, divorced, never married)	60	31.9
Economical situation		
Equal to monthly income	97	51.6
Less than monthly income	70	37.2
More than monthly income	21	11.2
Chronic disease		
Yes	166	88.3
No	22	11.7
With whom she/he lives		
Alone	37	19.7
With his wife and children	140	74.5
Other (caregiver, nursing home)	11	5.9
Frailty status		
Non-frail	62	33.0
Vulnerable	44	23.4
Mild Frailty	32	17.0
Moderate Frailty	32	17.0
Severe Frailty	18	9.6
Dialysis application		
Yes	35	18.6
No	153	81.4

* mean

Table 2. Relationship of some parameters with frailty

	Nonfrail N (%)	Vulnerable N (%)	Frail N (%)	EFS total (mean)
Gender				
Female	17 (18.5)	22 (23.9)	53 (57.6)	7.11±2.92
Male	45 (46.9)	22 (22.9)	29 (30.2)	5.3±2.87
Age*				
≥ 75 years	12 (41.0)	18 (21.3)	36 (37.7)	6.94±2.82*
< 75 years	50 (18.2)	26 (27.3)	46 (54.5)	5.78±3.07
Education*				
Primary school and Literate	38 (25.5)	36 (24.2)	75 (50.3)	6.67±3.00**
Middle and High School	12 (46.2)	7 (26.9)	7 (26.9)	4.88±2.59
University	12 (92.3)	1 (7.7)	0 (0)	3.23±1.30
Marital status*				
Married	48 (37.5)	29 (22.7)	51 (39.8)	5.84±2.91*
Not married	14 (23.3)	15 (25.0)	31 (51.7)	6.93±3.15
Economic situation*				
Equal to monthly income	35 (36.1)	25 (25.8)	37 (38.1)	5.71±2.64
Less than monthly income	14 (20.0)	14 (20.0)	42 (60.0)	7.51±3.21
More than monthly income	13 (61.9)	5 (23.8)	3 (14.3)	3.95±2.03**
Chronic disease*				
Yes	51 (30.7)	40 (24.1)	75 (45.2)	6.36±3.02*
No	11 (50.0)	4 (18.2)	7 (31.8)	4.91±2.8
With whom she/he lives*				
Alone	15 (40.5)	11 (29.7)	11 (29.7)	5.35±2.69
With his wife and children	47 (33.6)	30 (21.4)	63 (45.0)	6.21±3.06
Other (caregiver, nursing home)	0 (0)	3 (27.3)	8 (72.7)	8.73±2.41**
Dialysis application*				
Yes	5 (14.3)	7 (20.0)	23 (65.7)	7.91±3.17*
No	57 (37.3)	37 (24.2)	59 (38.6)	5.79±2.86
BMI*				
Normal-weight	16 (28.1)	13 (22.8)	28 (49.1)	6.67±3.25
Overweight	34 (44.7)	18 (23.7)	24 (31.6)	5.43±2.99**
Obese	12 (21.8)	13 (23.6)	30 (54.5)	6.73±2.66

* p≤0.05, ** Post-hoc test was applied.

When the relationship with frailty was evaluated, those whose income was more than their expenses were less frail (p=0.001), and frailty was higher in patients with chronic diseases other than CKD than those without (p=0.03). Frailty varied significantly with whom the patients lived with a caregiver or at a nursing home (p=0.04).

Although there was no difference in frailty assessment according to the CKD stage, frailty was significantly higher in dialysis patients than in nondialysis patients (p=0.001) (Table 2). According to the body mass index (BMI), there was a significant difference between the groups in terms of frailty (p=0.014). Overweight patients were less frail than obese and normal-weight subjects (p=0.029). Smoking was present in 93 (49%) patients. No relationship was found between smoking and frailty.

When the relationship between hemogram parameter variables and frailty was evaluated, it was

Table 3. Evaluation of the relationship between hemogram sub-parameter variables and frailty

	Nonfrail	Vulnerable	Frail
Hgb*	12.68±2.05	12.32±1.78	11.21±1.65*
Htc*	38.75±6.10	37.97±5.50	34.73±5.21*
WBC	8.22±1.98	8.28±1.76	7.64±2.46
Neutrophil	5.39±1.64	5.33±1.46	5.07±2.05
Lymphocyte	1.97±0.88	2.00±0.79	1.77±0.67
Monocyte	0.58±0.25	0.62±0.18	0.57±0.26
Platelet	250.77±70.66	252.70±61.66	243.74±81.41
MCV*	101.10±10.39	88.97±6.68	88.78±7.29
MCHC*	32.71±1.02*	32.18±1.63	32.32±1.01
RDW	14.50±1.57	14.54±1.63	15.18±2.36
MPV	9.74±0.78	9.76±0.88	9.79±0.79
PLR	1.46±0.75	1.44±0.65	1.50±0.68
NLR	3.31±2.25	3.20±1.27	3.44±2.67
LMR	3.76±1.59	3.31±1.27	3.68±2.32
RDW/MPV	1.49±019	1.50±.026	1.56±0.27
RDW/platelet	6.51±0.19	6.22±2.45	7.00±3.32
MPV/platelet	4.45±3.10	4.14±1.28	4.56±2.12
MPV/lymphocyte	5.87±2.72	5.76±2.74	6.75±5.19

* p≤0.05, Post-hoc test was applied.

Hgb:Hemoglobin, Htc: Hematocrit,WBC: white blood cell, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, RDW: Red blood cell distribution width, MPV:mean platelet volume, PLR: platelet-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, LMR: lymphocyte-monocyte ratio

observed that hemoglobin and hematocrit levels were significantly lower in the frail group (Table 3). When CKD stage and hemogram parameters were assessed, it was found that anemia was seen significantly more frequently as the CKD stage increased. As the stage raised, there was an increase in neutrophil/lymphocyte (N/L) and MPV/lymphocyte ratios and a decrease in lymphocyte/monocyte ratio (Table 4).

Linear multiple regression analysis was performed to determine the extent to which the variables of age, marital status, economic situation, presence of chronic illness, with whom they lived, dialysis application, and BMI predicted the total EFS score. As a result of the first model, R2 = 0.341 was found. Since this model was found to have a good fit (Durbin-Watson: 1.930), a seven-variable model was chosen, as shown in Table 5. Due to the high and significant autocorrelation value (r = 0.584,

Table 4. Evaluation of the relationship between hemogram sub-parameters and CKD stage

	Stage II (N=19)	Stage III (N=87)	Stage IV (N=46)	Stage V (N=36)
Hgb*	13.14±2.33	12.57±1.58	11.56±1.66	10.34±1.69*
Htc*	40.35±7.19	38.76.±4.53	35.74±5.09	31.61±5.24*
WBC*	6.72±0.71*	8.38±0.21*	8.19±0.16	7.52±0.26
Neutrophil*	4.05±0.15*	5.43±0.17*	5.28±0.21	5.31±0.21
Lymphocyte*	1.96±0.61	2.03±0.79	1.95±0.92	1.42±0.38*
Monocyte	0.50±0.17	0.58±0.23	0.61±0.21	0.62±.032
Platelet	232.68±73.39	259.09±70.80	233.91±64.58	248.11±87.47
MCV	87.74±8.04	97.55±8.72	89.81±7.10	88.27±5.42
MCHC	32.60±1.06	32.31±1.32	32.31±1.18	32.71±0.97
RDW	15.00±2.17	14.58±2.21	14.76±1.67	15.32±1.63
MPV	9.75±0.78	9.77±0.91	9.61±0.83	9.98±0.41
PLR	126.43±46.11	143.95±66.25	134.76±63.33	185.09±85.36
NLR*	2.25±1.20*	3.12±2.03	3.53±2.70	4.22±2.87*
LMR*	4.30±1.52	3.77±1.45	3.76±2.82	2.71±1.13*
RDW/MPV	1.56±0.36	1.50±0.28	1.54±0.17	1.53±0.16
RDW/platelet	7.20±3.24	5.98±1.64	7.52±5.80	6.89±2.36
MPV/platelet	4.54±1.25	4.08±1.30	4.96±4.06	4.52±1.55
MPV/lymphocyte*	5.45±1.71	5.56±2.32*	6.70±6.87	7.64±2.53*

* p≤0.05, Post-hoc test was applied.

Hgb: Hemoglobin, Htc: Hematocrit, WBC: white blood cell, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, RDW: Red blood cell distribution width, MPV:mean platelet volume, PLR:platelet-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, LMR: lymphocyte-monocyte ratio

Table 5. Linear regression table

	R2	β	p
Edmonton Frailty Scale	0.584		
Coefficient			0.021
Age (0 < 75, 1 ≥75)		0.982	0.156
Marital status (0 married, 1 not married)		-0.950	0.203
Economic situation (0 income>expenditure, 1 equal)		**3.143**	**<0.001**
Chronic Disease (0, not present, 1 present)		0.639	0.490
Living with/in (0 others, 1 nursing home)		0.226	0.857
Dialysis (0 No, 1 Yes)		**2.030**	**0.009**
BMI (0 overweight, 1 other)		0.912	0.145

p = 0.000), it was decided to keep the economic situation and dialysis application variables in the model (Table 5).

DISCUSSION

Chronic kidney disease is a progressive, irreversible, and chronic disease that progresses with multiple complications, causing mortality and severe morbidity. According to 2017 data, CKD caused 1.2 million deaths, and 7.6% (1.4 million) of all cardiovascular (CV) deaths can be attributed to impaired renal function. Of all-cause mortality globally, CKD and CV deaths attributable to CKD account for 4.6% (11).

In a study in Turkey, the frailty rate in geriatric patients was found to be 36.2%. While findings such as a high prevalence of comorbid diseases, being widowed, and increasing age were significant, no significant correlation was found between age and educational status (10). In our study, the frequency of frailty in the CKD population was 43.6%. In some frailty prevalence studies in general and CKD populations in the aged group in Turkey and other countries, the results were variable (up to 73%) (12-14). It was thought that different health system practices among governments, socio-economic conditions, geopolitical variability, and the use of different scales for analyzing frailty may have affected these variations in the results.

It is known that frailty is higher in CKD patients than in other populations, and frailty in HD patients has also been reported to be associated with increased mortality (14). Chronic kidney disease and frailty syndrome may present with similar symptoms and signs. Our study did not find a significant relationship between glomerular filtration rate (GFR) level and CKD stage and frailty.

The relationship between creatinine-based GFR measurements and frailty and cognitive dysfunction has not consistently been demonstrated in cohort studies. The reason for this has been shown to be the variability of creatinine between individuals and its direct relationship with parameters such as malnutrition-muscle mass (15). We evaluated the results of our study in this direction and considered the heterogeneity in creatinine-based GFR measurements in the foreground. However, although no correlation was found between the CKD stage and the degree of frailty, frailty was

significantly higher in our patients who underwent hemodialysis than in those who did not.

In an Australian study in which 909 patients aged 65 and over were evaluated, the frequency of frailty assessed with the Frailty Index was 48%. Low income, female gender, obesity, and living alone were significantly correlated (16). Although the geographical and living conditions were very different, this study's data were compatible with ours. Many studies conducted in other populations have shown that frailty is higher in women. Similar findings, specifically in the CKD population, suggest that the female gender may be associated with frailty, regardless of the underlying disease type (17).

The frequency of frailty and its higher incidence in patients over 75 years were similar to some studies in our country. In a recent study, Çelebi et al. found the prevalence of frailty to be 40.8% in patients over 65 undergoing hemodialysis. The mean dialysis time was longer in this study than in our study (12). In a study by Inoue et al. that included 630 patients with CKD over 70, frail patients were significantly older than the pre-frail and robust groups (mean age 83, 77, and 72, respectively) (18). In the cohort study by Johnson et al., the frequency of frailty was 67.7% in 2,275 dialysis patients, while this rate was 44.4% in patients < 40 years of age and 78.8% in patients aged < 80 years of age (19).

Lifelong continuity of treatment in chronic dialysis patients, transportation to the center 3 days a week, and complications, such as hypotension, cramps, nausea-vomiting, arrhythmias, catheter infections, and blood flow problems that may occur during and after HD adversely affect the patients and lead to a deterioration in their quality of life (20). Our study did not show that frailty increased as the CKD stage increased, but HD patients were found to be more frail. This finding may be important in predicting increased complications in the HD group. In addition, frailty is associated with an increase in the frequency of hospitalization and a deterioration in the quality of life. Yoneki et al. emphasized that frailty in HD patients is essential in predicting bone loss (21). In the study by Nixon et al., 450 patients were evaluated (84 of them HD patients), and the frequency of frailty was found to be 33%. According to the results, frail patients were older, but there was no relationship between gender differences or dialysis and frailty.

Conflicting results have been found in the literature on the BMI frailty relationship. In a study by Laur et al., there was no significant difference in BMI between frail and non-frail women, while it was lower in frail men than in non-frail women (22). Our study showed a significant difference in frailty between the groups according to BMI. Overweight patients were less frail than obese and normal-weight patients.

As expected, lower socio-economic status is associated with greater frailty in the geriatric patient group (16). Considering current socio-economic conditions, the fact that frailty was higher in low-income patients was considered a predictable result in our study and was consistent with the literature. The increase in frailty with a high number of comorbid diseases can be evaluated in a similar context (23).

In recent years, it has been frequently mentioned that some hemogram parameters are correlated with different variables in many other patient populations. Of these, N/L elevation has been shown to be associated with the risk of progression, increased mortality, and inflammation in the CKD population (24). Studies have shown that it can also predict frailty in the geriatric population (25). In our study, however, no significant relationship was found with frailty, but there was a significant relationship between increased CKD stage and N/L elevation.

As a result, we would like to emphasize that it would be rational to show a closer and more effective approach to frailty in advanced-aged, low-income female patients undergoing hemodialysis due to the high risk of mortality and morbidity. We believe

that the presence of trained personnel, especially in center dialysis units, early detection of frailty, and taking precautions can lead to positive results. Our study could not find a significant relationship between the CKD stage and frailty. However, we still think closer follow-up in patients in the risk group for CKD progression would be appropriate (especially in making HD indication decisions and because of the high risk of CKD progression in frail patients).

Our study has some limitations. Patients were evaluated based on frailty in line with the purpose of the study, and not including sarcopenia or malnutrition investigation was a limitation. Other limitations of our study were the lack of evaluation of cognitive functions and the low number of patients. There is no agreed-upon scale among frailty scales applied explicitly to the CKD population. We used the EFS, which is valid globally. Different prevalences of frailty can be determined from different scales regarding geographical, socio-economic, and cultural differences. Which one is valid for which population can be revealed by more comprehensive studies with a large number of patients in which different scales are compared simultaneously?

Conflict of interest

The authors declare that no conflicts of interest are associated with this study.

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