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Frailty is Independently Associated with Worse Health-Related Quality of Life in Chronic Kidney Disease: A Secondary Analysis of the 'Frailty Assessment in Chronic Kidney Disease' Study

Andrew C. Nixon MBChB[1-3], Theodoros M. Bampouras PhD[4,5], Neil Pendleton MBChB[6], Sandip Mitra MD[7,8], Mark E. Brady PhD[1], Ajay P. Dhaygude MD[1]

[1]Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom, [2]Centre for Health Research and Innovation, National Institute of Health Research Lancashire Clinical Research Facility, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom, [3]Division of Cardiovascular Sciences, University of Manchester, Manchester, United Kingdom, [4]Active Ageing Research Group, University of Cumbria, Lancaster, United Kingdom, [5]Lancaster Medical School, Lancaster University, Lancaster, United Kingdom, [6]Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, United Kingdom, [7]Manchester Academy of Health Sciences Centre, University of Manchester, Manchester, United Kingdom, [8]Devices for Dignity, National Institute of Health Research MedTech & In-vitro Diagnostics Co-operative, United Kingdom

Corresponding Author: Dr Andrew C. Nixon, Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Sharoe Green Lane,

Preston, PR2 9HT, UK. Phone 0044-1772523748; Fax 0044-1772523516; e-mail: andrew.nixon@lthtr.nhs.uk

List of Abbreviations

CI	Confidence Interval
CKD	Chronic kidney disease
CKD G4	Chronic kidney disease stage 4
CKD G5	Chronic kidney disease stage 5
CKD G5D	Dialysis-dependent chronic kidney disease
FI	Frailty Index
HRQOL	Health-related quality of life
IQR	Inter-quartile range
MMSE	Mini-Mental State Examination
SCREEN I	Seniors in the Community: Risk Evaluation for Eating and Nutrition Index
SD	Standard deviation
SPPB	Short Physical Performance Battery

ABSTRACT

Background

Understanding how frailty affects health-related quality of life (HRQOL) in those with chronic kidney disease (CKD) could assist in the development of management strategies to improve outcomes for this vulnerable patient group. This study aimed to evaluate the relationship between frailty and HRQOL in patients with CKD stage 4 and 5 (G4-5) and those established on haemodialysis (G5D).

Methods

Ninety participants with CKD G4-5D were recruited between December 2016 and December 2017. Frailty was assessed using the Frailty Phenotype, which included assessments of unintentional weight loss, weakness (handgrip strength), slowness (walking speed), physical activity and self-perceived exhaustion. HRQOL was assessed using the RAND 36-Item Health Survey Version 1.0 (SF-36).

Results

Nineteen (21%) patients were categorised as frail. Frailty, when adjusted for age, gender, dialysis-dependence and comorbidity, had a significant effect on five of the eight SF-36 domains: physical functioning, role limitations due to emotional problems, energy/fatigue, social functioning and pain. Regression modelling best explained the variation in the physical functioning domain (adj. $R^2 = 0.27$, $p < 0.001$), with frailty leading to a 26-point lower score. Exhaustion was the only Frailty Phenotype component that had a significant effect on scores across all SF-36 domains.

Conclusions

Frailty is independently associated with worse HRQOL in patients with CKD G4-5D, with self-perceived exhaustion being the most significant Frailty Phenotype component contributing to HRQOL. Efforts should be made to identify frail patients with CKD so that management strategies can be offered that aim to improve morbidity, mortality and patient-reported outcomes, including HRQOL and fatigue.

Keywords: Frailty; Quality of Life; Geriatric Nephrology; Chronic Kidney Disease; End Stage Kidney Disease; Haemodialysis

INTRODUCTION

Frailty is the result of a sustained deterioration in multiple physiological processes that leads to a state of increased vulnerability associated with disability, hospitalisations and an increased mortality risk [1]. The prevalence of frailty is markedly higher in those with chronic kidney disease (CKD) than in the general older population [2,3]. The trajectory from robustness to frailty is associated with progressive renal impairment, with significant muscle wasting, a major contributor to physical frailty in CKD patients, occurring prior to the commencement of dialysis [4-6]. Importantly, frailty is an independent risk factor for falls, hospitalisation and death in those with CKD [2,4,7-14].

Irrespective of frailty status, patients with CKD have a considerable symptom burden, high healthcare utilisation and poor health-related quality of life (HRQOL) [15-18]. Though frailty is linked with worse HRQOL in the general older population, the relationship between frailty and HRQOL is less certain in those with CKD [19]. The Frailty Phenotype is an operationalised definition of the construct of frailty and has been well studied in CKD cohorts [1,2]. It is a composite measure that involves 5 distinct components, including assessments of unintentional weight loss, weakness, slowness, physical activity and exhaustion. The relative significance of these individual components on HRQOL in patients with CKD is not known. Understanding how frailty and its components affect HRQOL in those with CKD could assist in the development of targeted management strategies to improve outcomes for this vulnerable patient group.

The purpose of this study was to: (1) evaluate the relationship between frailty, categorised by the Frailty Phenotype, and HRQOL; and (2) assess the relative significance of individual components of the Frailty Phenotype on HRQOL in patients with CKD stage 4 and 5 (G4-5) and those established on haemodialysis (G5D).

MATERIALS AND METHODS

Study Design and Participant Selection

This was a secondary analysis of data from the 'Frailty Assessment in Chronic Kidney Disease' study that evaluated the diagnostic accuracy of frailty screening methods in a cohort of patients with advanced CKD [20]. Participants were recruited from nephrology outpatient clinics and two Haemodialysis Units at Lancashire Teaching Hospitals NHS Foundation Trust between December 2016 and December 2017. Patients ≥18 years old with CKD G4-5D were eligible for participation in the study. Exclusion criteria included patients who had a lower limb amputation, metastatic carcinoma, unstable angina or who had a been diagnosed, in the preceding 3 months, with a myocardial infarction, transient ischaemic attack or stroke. Written informed consent was obtained for all participants. Ethical approval was obtained from the NHS Health Research Authority (IRAS ID 216379) and the study was conducted in accordance with the Declaration of Helsinki.

Data Collection

Baseline Data: Baseline demographic and clinical characteristic data was collected from medical records and during participant interview and assessment. This data included age, height, weight, co-morbidities, medication history, smoking history, blood pressure, falls history and laboratory variables.

Charlson Comorbidity Index: A Charlson Comorbidity Index (CCI) score was calculated for all participants [21]. The CCI is a commonly used assessment of comorbidity that is predictive of outcomes in CKD populations [22-24].

Karnofsky Performance Status Scale: A Karnofsky Performance Status Scale assessment, providing a measure of perceived performance that has been well-studied in CKD cohorts, was performed on all participants by a clinician [25,26].

Mini-Mental State Examination: The Mini-Mental State Examination (MMSE), a widely-used screening tool for cognitive impairment, was performed on all participants [27,28]. A cut-off $\leq$27 has a higher sensitivity for identifying cognitive impairment in symptomatic populations than the conventional cut-off of <24 [27].

Seniors in the Community: Risk Evaluation for Eating and Nutrition Index: All participants completed the Seniors in the Community: Risk Evaluation for Eating and Nutrition Index (SCREEN I), which is a validated nutritional risk screening tool for community-dwelling older adults [29,30]. A score $\leq$50 has been suggested to identify individuals at nutritional risk [30].

Frailty Assessment: Frailty was assessed using the Frailty Phenotype, which included assessments of unintentional weight loss, weakness (hand grip strength), slowness (walking speed), physical activity and self-perceived exhaustion. Frailty was diagnosed if 3 or more Frailty Phenotype components were present [1]:

1. The unintentional weight loss component was defined as a loss of ≥10 pounds or ≥5% body weight over the preceding 12 months [1].

2. Hand grip strength (Takei 5101 GRIP-D dynamometer, Takei Scientific Inst. Co. Ltd., Niigata, Japan) was assessed in the seated position with the elbow positioned at 90 degrees, supported by the arm of a chair, and the dynamometer supported by the assessor [31]. Both arms were examined with the highest score from three efforts from each side being used for analysis. The body mass index and gender stratified hand grip strength cut-offs proposed by the Fried Frailty Phenotype were used to describe weakness [1].

3. Walking speed was assessed by asking participants to walk 15 feet (4.57m) at their normal walking pace on two occasions. Participants were advised to use their walking aid, if they normally used one. Infrared timing gates (Brower Timing System 2012, Brower Timing Systems, Draper, UT, USA) were used to record walking time. The fastest of two trials was used for analysis. Participants physically unable to complete the assessment were assigned the slowest time from within the cohort. The height and gender stratified walking speed cut-offs suggested by the Fried Frailty Phenotype were used to describe slowness [1].

4. Physical activity was assessed using a modified version of the Minnesota Leisure Time Questionnaire [32]. Low physical activity was defined as <383 kcals per week for men and <270 kcals per week for women [1].

5. Participants were read two statements from the Center for Epidemiological Studies Depression Scale to assess self-perceived exhaustion: (1) I felt that everything I did was an effort. (2) I could not get going [33]. Participants were then asked, 'How often did you feel this?' and provided the following scale: 0 = rarely or none of the time, 1 = some of the time, 2 = moderate amount of the time, 3 = most of the time. Self-perceived exhaustion was described if an answer $\geq$2 was given for either statement [1].

Health-Related Quality of Life: HRQOL was assessed using the RAND 36-Item Health Survey Version 1.0 (SF-36), which is validated in general and CKD populations [34-38]. The SF-36 consists of 36 questions and assesses 8 domains of HRQOL: physical functioning, role limitations due to physical problems, role limitations due to emotional problems, emotional well-being, social functioning, energy/fatigue, pain and general health perceptions [34]. The answers to designated questions are transformed to create scores for HRQOL domains. The domain scores range from 0 to 100, with lower scores indicating worse HRQOL [34,35]. The SF-36 also asks 'Compared to one year ago, how would you rate your health in general now?'. Participants answer on a 1-5 scale, with 1 being 'much better now than one year ago' and 5 being 'much worse now than one year ago'.

Statistical Analysis

As a secondary analysis, no prospective sample size calculation was performed for the outcomes reported. Descriptive statistics were used to summarise demographic and clinical characteristic data. Pearson's (for continuous data) or Spearman's Correlation (for ordinal data) was used to assess the correlation between SF-36 domain scores and age and the

Frailty Phenotype and CCI scores. Multiple linear regression was used to assess the magnitude of association between frailty and SF-36 domain scores, adjusting for age, gender, dialysis-dependence and CCI scores, as well as, the magnitude of the association between Frailty Phenotype components and SF-36 domain scores. A p value <0.05 was considered statistically significant. All statistical analyses were performed on IBM SPSS Statistics Software (version 24, IBM Corp).

RESULTS

Ninety participants completed the Frailty Phenotype assessment. Table 1 demonstrates the demographics and clinical characteristics of the overall cohort and of non-frail and frail participants. Nineteen (21%) participants were categorised as frail. Figure 1 illustrates the prevalence of Frailty Phenotype components.

Participant Characteristics and HRQOL

Mean SF-36 scores divided by frailty status, Frailty Phenotype components, age </≥65 years, gender and dialysis-dependence are shown in Table 2. Frail participants had significantly lower mean SF-36 scores in the following domains: physical functioning, role limitations due to physical health, energy/fatigue, social functioning and pain. Participants categorised as weak or slow also had significantly lower scores in these SF-36 domains. In addition to these domains, participants with low physical activity had significantly lower scores in the role limitations due to emotional problems domain. Those categorised as suffering from exhaustion had significantly lower scores across all SF-36 domains, whereas there was no significant difference in the mean SF-36 domain scores for participants who reached the unintentional weight loss threshold. Only participants categorised as weak had significantly higher (worse) median scores for the question regarding health change.

Participants <65 years old had significantly lower SF-36 scores in the following domains: role limitations due to emotional problems, energy/fatigue and general health. Female participants had significantly lower scores in the physical functioning and energy/fatigue SF-

36 domains. Participants receiving dialysis only had significantly lower scores in the physical functioning SF-36 domain.

Correlation Between HRQOL and Frailty, Age and Comorbidity

Table 3 demonstrates the correlation between SF-36 domains and Frailty Phenotype Score, age and CCI score. There was a significant negative correlation between all domain scores of the SF-36, except the general health domain, and Frailty Phenotype score. The correlation coefficients indicated a strong association between the physical functioning and energy/fatigue domain scores and the Frailty Phenotype score. There was a moderate association between the social functioning and pain domain scores and the Frailty Phenotype score. There was a significant positive correlation, though the coefficients revealed a weak association, between age and the following domain scores: role limitations due to emotional problems, emotional well-being, social functioning and general health. There was a significant negative correlation between CCI score and the SF-36 pain domain score; again, this coefficient only suggested a weak association.

Influence of Frailty on HRQOL

Regression analyses assessing the magnitude of the association between frailty and SF-36 domains are presented in Table 4. Frailty, when adjusted for age, gender, dialysis-dependence and CCI score, had a significant effect on the following SF-36 domains: physical functioning, role limitations due to emotional problems, energy/fatigue, social functioning,

and pain. Regression modelling best explained the variation in the physical functioning domain score, with frailty leading to a 26-point lower score.

Regression analyses assessing the magnitude of the association between Frailty Phenotype components and SF-36 domains are displayed in Table 5. Self-perceived exhaustion was the only Frailty Phenotype component that had a significant effect on scores across all SF-36 domains. Unintentional weight loss did not have a significant effect on any of the SF-36 domain scores. Low physical activity had significant effects on physical functioning, role limitations due to emotional problems, energy/fatigue and social functioning domains. Weakness had a significant effect on the physical functioning and general health domains, whereas slowness only had a significant effect on the pain domain.

DISCUSSION

To our knowledge, this is the first study that explores the relationship between frailty, as categorised by the original Frailty Phenotype, and HRQOL in those with CKD G4-5 and CKD G5D. Furthermore, it is the first study that assesses the relative significance of individual Frailty Phenotype components on HRQOL in this distinct patient group. Studies by Mansur et al and Lee et al have demonstrated that frailty is associated with worse HRQOL in those with CKD [13,14]. However, both studies used a modified version of Frailty Phenotype to categorise frailty, replacing objective measures of grip strength and walking speed with a self-report assessment of physical function [13,14]. Such an approach has been shown to substantially over-estimate the prevalence of frailty [39]. Furthermore, the self-report assessment used was the physical functioning domain of the SF-36, which was also used within the assessment of HRQOL [13,14,35] Additionally, the 'vitality domain' of the SF-36 was used to determine the exhaustion component of their modified Frailty Phenotype [13,14,35]. Therefore, it is difficult to interpret the findings given the overlap of the frailty and HRQOL assessments. Iyasere et al demonstrated that frailty was associated with worse HRQOL, symptom burden and depression scores in those with dialysis-dependent CKD [40]. Their study used the Clinical Frailty Scale that relies upon a healthcare professional's assessment of frailty based upon descriptors of levels of frailty [41]. Though not as well-studied as the Frailty Phenotype in CKD populations, the Clinical Frailty Scale has been shown to be an accurate screening tool for frailty (identified by the Frailty Phenotype) [20] and predictive of mortality in patients with CKD [24,42].

Our study confirms that frailty is significantly associated with worse HRQOL in patients with CKD G4-5D. Frailty Phenotype scores correlated with 7 of the 8 domains of the SF-36. Frail participants had significantly lower mean scores across 5 of the 8 domains, specifically physical functioning, role limitations due to physical health, energy/fatigue, social functioning and pain domains. When adjusted for age, gender, dialysis-dependence and CCI, frailty was independently associated with at least a 20-point lower score in physical functioning, role limitations due to emotional problems, energy/fatigue, social functioning and pain SF-36 domains. Notably, when adjusting for frailty, burden of comorbidity had no effect on SF-36 scores. Older age was not associated with worse HRQOL, in fact older age was associated with a modest improvement in several SF-36 domains. This relationship has been reported previously and is perhaps due to changes in emotional regulation with age [43-45]. Female participants had worse HRQOL, specifically in physical functioning and energy/fatigue domains, a finding that has been reported elsewhere in the literature [43,46,47]. However, there was no significant effect noted within the regression model that included frailty. Frailty was an independent predictor of poor HRQOL in this advanced CKD cohort, highlighting the importance of the construct of frailty, over and above more traditional predictors of HRQOL [43], and emphasising the importance of frailty screening in advanced CKD populations.

Participants categorised as exhausted, regardless of whether they were classified as frail overall, had lower mean scores across all SF-36 domains. Depending on the SF-36 domain, the exhaustion Frailty Phenotype component was associated with 10- to 46-point lower score. Studies within the general older population have also found that this domain had the greatest effect on HRQOL [47,48]. Exhaustion, also known as fatigue, is a commonly

reported and especially problematic symptom in patients with advanced CKD, particularly for those receiving dialysis [49-51]. Fatigue is not only associated with worse HRQOL, but also survival in advanced CKD, with the HEMO study demonstrating that an increase of 10-points in 'vitality score' was associated with a 10% increase in mean survival [52,53]. Accordingly, addressing the causes of fatigue may be associated with improved HRQOL and survival in non-frail and frail patients alike. This is a challenging undertaking, as fatigue is a complex multi-dimensional and multi-factorial issue [50]. Appropriate management of renal anaemia, adequate nutrition and prompt management of concurrent medical problems is essential [50]. However, there is also an association between fatigue and psychological distress, therefore therapies that address mood and anxiety issues, may also be associated with an improvement in fatigue symptoms [50,54]. Sleep disorders are common in those with advanced CKD [55]. Cognitive behavioural therapy leads to improved sleep quality and reduced fatigue, thus it may be a useful therapy for frail patients with CKD [56]. Furthermore, low physical activity levels are associated with increased levels of fatigue [57]. Exercise improves fatigue in the general population and has been shown to improve HRQOL and fatigue in those with advanced CKD [58-60]. Evidence to-date suggests that exercise training can improve physical function and HRQOL in frail older adults [61-63]. However, studies have not targeted pre-frail and frail patients with CKD, a group of patients who are typically poorly represented in interventional studies [64,65]. Further evidence is needed on the feasibility of a rehabilitation programme for frail patients with advanced CKD. Ultimately, management strategies likely need to be multimodal and multidisciplinary, including nutritional, psychological and rehabilitation components [50,66]. Additional evaluation of the relationship between fatigue and HRQOL in frail advanced CKD

populations is needed, particularly to assess the relative contributions of physical capacity and psychological well-being.

There are acknowledged limitations of this study. Firstly, the cross-sectional study design does not allow for conclusions to be made on causation. Longitudinal studies are required to assess for a causal relationship between frailty and HRQOL. Secondly, further investigation within more culturally diverse populations is needed given that participants within this study were recruited from a single-centre with a predominantly White British population. Finally, this is a secondary analysis of a study that was powered to assess the diagnostic accuracy of frailty screening methods in advanced chronic kidney disease, therefore the results presented in this analysis should be interpreted judiciously.

Conclusions

Frailty is independently associated with worse HRQOL in patients with CKD G4-5D. Exhaustion, or fatigue, is the most significant Frailty Phenotype component contributing to worse HRQOL in those with advanced CKD. Efforts should be made to identify frail patients with CKD so that management strategies can be offered that aim to improve morbidity, mortality and patient-reported outcomes, including HRQOL and fatigue. Additional study is needed to determine the most significant contributors to fatigue in frail patients with advanced CKD so that treatment can be tailored for this vulnerable group of patients.

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CONFLICT OF INTEREST STATMENT

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The results presented in this paper have not been published previously in whole or part, except in abstract form. Preliminary data was published in the American Society of Nephrology Kidney Week 2017 Conference Abstract Supplement. This study is a secondary analysis of the 'Frailty Assessment in CKD' study [20]. Demographic and clinical characteristic data is the same in both manuscripts as data was collected from the same cohort.

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TABLES

Table 1. Participant Baseline Demographic and Clinical Characteristic Data.

	Overall (n=90)	Non-Frail (n=71)	Frail (n=19)
Age (years)	69 (±13)	68 (±13)	73 (±11)
Female, n (%)	45 (50)	30 (42)	15 (79)
BMI (kg/m^2)	29 (±6)	29 (±6)	28 (±6)
CKD Stage			
- **CKD G4-5, n (%)**	60 (67)	51 (72)	9 (47)
- **CKD G5D, n (%)**	30 (33)	20 (28)	10 (53)
CCI, median (IQR)	3 (2)	3 (2)	4 (4)
Diabetes Mellitus, n (%)	24 (27)	16 (23)	8 (42)
Karnofsky Score, median (IQR)	70 (30)	80 (20)	60 (20)
Medications	9 (±4)	8 (±3)	11 (±5)
Current or ex-smoker, n (%)	49 (54)	40 (56)	9 (47)
MMSE Score ≤27*, n (%)	18 (20)	13 (19)	5 (29)
Fall within last 6 months, n (%)	16 (18)	11 (15)	5 (26)
SCREEN I Score ≤50, n (%)	70 (78)	53 (75)	17 (89)
Blood Pressure (mmHg)			
- **Systolic**	148 (±20)	148 (±19)	149 (±25)
- **Diastolic**	72 (±14)	74 (±14)	67 (±15)
Laboratory Variables			
- **Haemoglobin (g/L)**	116.3 (±13.3)	117.6 (±12.7)	111.4 (±14.6)
- **White Cell Count (x 10^9/L)**	7.7 (±2.5)	7.6 (±2.5)	8.0 (±2.6)
- **CRP** (mg/L), median (IQR)**	5.3 (10.0)	5.0 (10.7)	5.5 (8.4)
- **Albumin (g/L)**	40.9 (±3.3)	41.3 (±3.3)	39.6 (±3.3)
- **Total Protein (g/L)**	67.4 (±5.6)	67.7 (±5.3)	66.2 (±6.6)

Data presented as mean (± SD) unless otherwise specified. *MMSE data was available for 87 participants. **CRP data was available for 64 participants. BMI, Body Mass Index. CCI, Charlson Comorbidity Index. MMSE, Mini-Mental State Examination. SCREEN I, Seniors in the Community: Risk Evaluation for Eating and Nutrition Index. CRP, C-Reactive Protein.

Table 2. SF-36 Scores divided by Frailty Status, Frailty Criteria Component, Age (< or ≥65 years), Gender and Dialysis-Dependence.

	Physical Functioning	Role Limitations Due to Physical Health	Role Limitations Due to Emotional Problems	Energy/Fatigue	Emotional Well-Being	Social Functioning	Pain	General health	Change in Health
Frail Status									
- Non-Frail	58.1 (±29.5)	45.5 (±43.9)	63.4 (±40.7)	47.6 (±22.5)	74.8 (±19.5)	74.3(±29.6)	68.7 (±26.8)	28.9 (±18.6)	3.0 (1.0)
- Frail	22.9 (±21.7)*	21.1 (±28.0)**	45.6 (±50.0)	27.1 (±17.1)*	67.9 (±24.8)	52.0 (±31.5)**	39.2 (±27.1)*	27.6 (±19.0)	4.0 (2.0)
Weight Loss									
- Non-Frail	52.4 (±31.4)	41.4 (±43.0)	59.8 (±42.5)	44.2 (±23.4)	74.1 (±20.7)	69.6 (±31.5)	63.3 (±29.0)	30.0 (±18.3)	3.0 (1.0)
- Frail	30.7 (±25.7)	28.6 (±30.4)	57.1 (±53.5)	32.9 (±14.4)	64.1 (±21.1)	69.6 (±29.6)	52.5 (±33.7)	35.7 (±20.9)	3.0 (2.0)
Weakness									
- Non-Frail	63.8 (±28.1)	49.5 (±43.1)	64.5 (±43.1)	48.7 (±24.5)	73.7 (±21.9)	76.3 (±31.7)	69.4 (±28.1)	27.0 (±18.4)	3.0 (1.0)
- Frail	36.3 (±28.6)*	30.4 (±39.2)***	54.3 (±43.0)	37.3 (±19.9)***	73.0 (±19.8)	62.2 (±29.3)***	54.9 (±29.1)***	30.3 (±18.8)	4.0 (1.0)**
Slowness									
- Non-Frail	58.1 (±29.3)	45.5 (±43.5)	61.0 (±42.2)	48.0 (±22.1)	75.2 (±19.3)	73.4 (±30.0)	70.1 (±25.7)	29.5 (±18.3)	3.0 (2.0)
- Frail	22.9 (±22.3)*	21.1 (±30.3)**	54.3 (±47.4)	25.5 (±17.2)*	66.7 (±25.0)	55.3 (±32.6)***	33.9 (±24.2)*	25.3 (±19.5)	4.0 (1.0)
Physical Activity									
- Non-Frail	59.2 (±29.3)	47.4 (±44.1)	69.0 (±38.42)	51.5 (±21.2)	76.0 (±18.7)	78.0 (±28.0)	68.1 (±26.8)	30.8 (±31.3)	3.0 (1.3)
- Frail	35.3 (±29.6)*	27.6 (±35.5)***	42.7 (±46.6)**	28.4 (±18.5)*	68.6 (±23.6)	54.3 (±31.4)*	52.3 (±31.3)**	24.7 (±15.9)	4.0 (1.8)
Exhaustion									
- Non-Frail	65.7 (±30.0)	54.5 (±42.4)	76.9 (±33.4)	56.4 (±17.0)	79.8 (±15.7)	81.7 (±26.3)	78.1 (±19.7)	32.1 (±18.7)	3.0 (1.0)
- Frail	30.2 (±25.0)*	21.1 (±33.7)*	36.0 (±44.1)*	25.3 (±17.3)*	64.5 (±23.7)*	53.0 (±30.1)*	41.1 (±26.8)*	23.8 (±17.4)***	3.5 (2.0)
Age									
- <65 years	49.8 (±30.9)	35.2 (±42.3)	43.2 (±46.1)	33.1 (±24.8)	67.4 (±25.1)	57.4 (±36.1)	56.9 (±32.4)	21.3 (±14.7)	3.0 (2.0)
- ≥65 years	51.1 (±31.9)	42.6 (±42.2)	66.7 (40.2)***	47.6 (±20.9)***	75.9 (±18.3)	74.8 (±27.6)	64.9 (±27.8)	31.7 (±19.2)**	3.0 (1.0)
Gender									
- Male	60.3 (±29.7)	45.0 (±42.5)	57.8 (±43.5)	48.6 (±21.7)	74.8 (±21.0)	74.4 (±27.8)	66.3 (±27.5)	31.4 (±20.2)	3.0 (1.5)
- Female	41.1 (±30.4)**	35.7 (±41.8)	61.5 (±43.2)	38.0 (±23.2)***	72.0 (±21.0)	64.7 (±34.0)	58.7 (±30.9)	25.8 (±16.4)	3.0 (1.5)
CKD Stage									
- CKD G4-5	58.5 (±29.9)	44.3 (±42.5)	62.8 (±42.6)	44.9 (±22.7)	74.4 (±20.8)	72.7 (±31.2)	64.8 (±28.3)	29.5 (±19.7)	3.0 (1.0)
- CKD G5D	35.1 (±28.8)*	32.8 (±41.1)	53.3 (±44.3)	40.0 (±23.5)	71.3 (±21.1)	63.3 (±31.0)	58.0 (±31.3)	26.9 (±16.1)	2.0 (1.0)

Data presented as mean (±SD) or median (IQR). *<0.001; **<0.01; ***<0.05.

Table 3. Correlation between SF-36 Domains and Frailty Phenotype Score, Age and Charlson Comorbidity Index Score.

	Physical Functioning	Role Limitations Due to Physical Health	Role Limitations Due to Emotional Problems	Energy/Fatigue	Emotional Well-Being	Social Functioning	Pain	General Health
Frailty Phenotype Score, rho	-0.65* (0.77 to -0.50)	-0.38* (-0.55 to -0.20)	-0.35** (-0.54 to -0.15)	-0.65* (-0.76 to -0.51)	-0.27** (-0.47 to -0.06)	-0.52* (-0.68 to -0.33)	-0.53* (-0.68 to -0.36)	-0.11 (-0.31 to 0.11)
Age, r	-0.05 (-0.24 to 0.15)	0.01 (-0.20 to 0.22)	0.29** (0.08 to 0.48)	0.17 (-0.06 to 0.39)	0.23*** (0.01 to 0.42)	0.25*** (0.02 to 0.46)	0.08 (-0.14 to 0.30)	0.22*** (0.03 to 0.41)
CCI Score, rho	-0.14 (-0.34 to 0.08)	-0.18 (-0.38 to 0.02)	0.06 (-0.16 to 0.27)	-0.09 (-0.30 to 0.13)	0.07 (-0.14 to 0.28)	-0.09 (-0.31 to 0.13)	-0.24*** (-0.43 to -0.04)	-0.01 (-0.23 to 0.21)

Data presented as correlation coefficient (95% confidence interval). *<0.001; **<0.01; ***<0.05. CCI, Charlson Comorbidity Index.

Table 4. Regression Analyses Assessing the Influence of Frailty, Age, Gender, Dialysis-Dependence and Comorbidity on SF-36 Domains.

SF-36 Domain	Unstandardised β Coefficient	Standardised β Coefficient	P Value
Physical Functioning Adj. R^2 = 0.27, p <0.001			
- Frail	-25.75 (-41.19 to -10.32)	-0.34	0.001
- Age	-0.05 (-0.51 to 0.41)	-0.02	0.82
- Female	-10.01 (-22.06 to 2.04)	-0.16	0.1
- Dialysis	-17.49 (-30.29 to -4.69)	-0.26	0.01
- CCI	-1.71 (-5.95 to 2.53)	-0.08	0.42
Role Limitations Due to Physical Health Adj. R^2 = 0.04, p = 0.13	-	-	-
Role Limitations Due to Emotional Problems Adj. R^2 = 0.10, p = 0.02			
- Frail	-28.74 (-52.24 to -5.23)	-0.27	0.02
- Age	1.05 (0.35 to 1.75)	0.32	0.004
- Female	9.59 (-8.75 to 27.94)	0.11	0.3
- Dialysis	0.22 (-19.26 to 19.71)	0.002	0.98
- CCI	2.46 (-3.99 to 8.92)	0.08	0.45
Energy/Fatigue Adj. R^2 = 0.16, p = 0.001			
- Frail	-20.28 (-32.33 to -8.22)	-0.36	0.001
- Age	0.46 (0.10 to 0.82)	0.26	0.01
- Female	-6.90 (-16.31 to 2.51)	-0.15	0.15
- Dialysis	2.35 (-7.64 to 12.34)	0.05	0.64
- CCI	-0.97 (-4.28 to 2.34)	-0.06	0.56
Emotional Well-Being Adj. R^2 = 0.05, p = 0.09	-	-	-
Social Functioning Adj. R^2 = 0.14, p = 0.004			
- Frail	-23.41 (-40.07 to -6.74)	-0.31	0.01
- Age	0.75 (0.25 to 1.24)	0.31	0.003
- Female	-5.31 (-18.32 to 7.70)	-0.09	0.42
- Dialysis	-0.36 (-14.17 to 13.46)	-0.01	0.96
- CCI	-1.21 (-5.79 to 3.37)	-0.05	0.6
Pain Adj. R^2 = 0.18, p = 0.001			
- Frail	-28.08 (-43.33 to -12.83)	-0.39	<0.001
- Age	0.40 (-0.06 to 0.85)	0.18	0.09
- Female	-2.02 (-13.93 to 9.88)	-0.04	0.74
- Dialysis	-0.16 (-12.81 to 12.48)	-0.003	0.98
- CCI	-3.82 (-8.01 to 0.37)	-0.18	0.07
General Health Adj. R^2 = 0.02, p = 0.23	-	-	-

Adj. R^2, Adjusted R^2; CCI, Charlson Comorbidity Index.

Table 5. Regression Analyses Assessing the Influence of Frailty Phenotype Components on SF-36 Domains.

SF-36 Domain	Unstandardised β Coefficient	Standardised β Coefficient	P Value
Physical Functioning			
Adj. R^2 = 0.40, p <0.001			
- Weight Loss Frail	-3.55 (-24.00 to 16.90)	-0.03	0.73
- Weakness Frail	-11.89 (-23.41 to -0.37)	-0.19	0.04
- Slowness Frail	-12.63 (-28.04 to 2.79)	-0.17	0.11
- Physical Activity Frail	-11.76 (-23.11 to -0.40)	-0.18	0.04
- Exhaustion Frail	-22.85 (-34.91 to -10.79)	-0.36	<0.001
Role Limitations Due to Physical Health			
Adj. R^2 = 0.13, p = 0.01			
- Weight Loss Frail	0.17 (-32.93 to 33.28)	0.001	0.99
- Weakness Frail	-4.82 (-23.47 to 13.83)	-0.06	0.61
- Slowness Frail	-4.07 (-29.03 to 20.89)	-0.04	0.75
- Physical Activity Frail	-10.38 (-28.76 to 8.01)	-0.12	0.27
- Exhaustion Frail	-27.44 (-46.97 to -7.91)	-0.32	0.01
Role Limitations Due to Emotional Problems			
Adj. R^2 = 0.26, p <0.001			
- Weight Loss Frail	-0.26 (-31.53 to 31.01)	-0.002	0.99
- Weakness Frail	5.26 (-12.35 to 22.87)	0.06	0.55
- Slowness Frail	22.88 (-0.69 to 46.45)	0.22	0.06
- Physical Activity Frail	-21.00 (-38.36 to -3.64)	-0.23	0.02
- Exhaustion Frail	-46.12 (-64.56 to -27.67)	-0.53	<0.001
Energy/Fatigue			
Adj. R^2 = 0.54, p <0.001			
- Weight Loss Frail	-0.07 (-13.19 to 13.06)	-0.001	0.99
- Weakness Frail	3.96 (-3.43 to 11.36)	0.09	0.29
- Slowness Frail	-4.34 (-14.23 to 5.55)	-0.08	0.39
- Physical Activity Frail	-15.56 (-22.85 to -8.27)	-0.33	<0.001
- Exhaustion Frail	-27.30 (-35.04 to -19.56)	-0.59	<0.001
Emotional Well-Being			
Adj. R^2 = 0.12, p = 0.01			
- Weight Loss Frail	-6.29 (-22.68 to 10.10)	-0.08	0.45
- Weakness Frail	7.21 (-2.03 to 16.44)	0.17	0.12
- Slowness Frail	0.07 (-12.29 to 12.43)	0.001	0.99
- Physical Activity Frail	-4.51 (-13.61 to 4.59)	-0.10	0.33
- Exhaustion Frail	-16.56 (-26.23 to -6.90)	-0.40	0.001

Table 5. ***Continued.***

SF-36 Domain	Unstandardised β Coefficient	Standardised β Coefficient	P Value
Social Functioning			
Adj. R^2 = 0.24, p <0.001			
- Weight Loss Frail	10.02 (-12.89 to 32.93)	0.09	0.39
- Weakness Frail	-1.35 (-14.26 to 11.56)	-0.02	0.84
- Slowness Frail	-0.87 (-18.14 to 16.40)	-0.01	0.92
- Physical Activity Frail	-16.89 (-29.61 to -4.16)	-0.26	0.01
- Exhaustion Frail	-24.62 (-38.14 to -11.11)	-0.39	<0.001
Pain			
Adj. R^2 = 0.44, p <0.001			
- Weight Loss Frail	10.71 (-7.69 to 29.10)	0.10	0.25
- Weakness Frail	4.64 (-5.73 to 15.00)	0.08	0.38
- Slowness Frail	-23.57 (-37.44 to -9.71)	-0.33	0.001
- Physical Activity Frail	-3.12 (-13.33 to 7.10)	-0.05	0.55
- Exhaustion Frail	-30.41 (-41.27 to -19.56)	-0.52	<0.001
General Health			
Adj. R^2 = 0.08, p = 0.04			
- Weight Loss Frail	11.17 (-3.82 to 26.16)	0.16	0.14
- Weakness Frail	8.67 (0.23 to 17.12)	0.24	0.04
- Slowness Frail	-3.73 (-15.03 to 7.57)	-0.08	0.51
- Physical Activity Frail	-4.62 (-12.94 to 3.70)	-0.12	0.27
- Exhaustion Frail	-10.36 (-19.20 to -1.52)	-0.28	0.02

Adj. R^2, Adjusted R^2.

FIGURE LEGEND

Figure 1. Prevalence of Frailty Phenotype Components.

FIGURE