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ORIGINAL ARTICLE

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

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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 Stages 4 and 5 (G4–5) and those established on haemodialysis (G5D).

Methods. Ninety participants with dialysis-dependent chronic kidney disease (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 categorized 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.

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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: chronic kidney disease, end-stage kidney disease, frailty, geriatric nephrology, haemodialysis, quality of life

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INTRODUCTION

Frailty is the result of a sustained deterioration in multiple physiological processes that leads to a state of increased vulnerability associated with disability, hospitalizations 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, hospitalization and death in those with CKD [2, 4, 7–14].

Irrespective of frailty status, patients with CKD have a considerable symptom burden, high health care utilization and poor health-related quality of life (HRQOL) [15–18]. Although 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 operationalized definition of the construct of frailty and has been well studied in CKD cohorts [1, 2]. It is a composite measure that involves five 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 (i) evaluate the relationship between frailty, categorized by the Frailty Phenotype, and HRQOL and (ii) assess the relative significance of individual components of the Frailty Phenotype on HRQOL in patients with CKD Stages 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 National Health Service (NHS) Foundation Trust between December 2016 and December 2017. Patients ≥18 years of age 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 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 demographic and clinical characteristics data were collected from medical records and during the participant interview and assessment. These data included age, height, weight, comorbidities, medication history, smoking history, blood pressure, falls history and laboratory variables.

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].

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].

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

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 ≤50 has been suggested to identify individuals at nutritional risk [30].

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 three 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 Instruments Co., 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 original Frailty Phenotype were used to describe weakness [1].
3. Walking speed was assessed by asking participants to walk 15 ft (4.57 m) 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

Table 1. Participant baseline demographic and clinical characteristics data

Characteristics	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[a], *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 (×10^9/L)	7.7 ± 2.5	7.6 ± 2.5	8.0 ± 2.6
CRP[b] (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 ± standard deviation unless otherwise specified.. [a]MMSE data were available for 87 participants.. [b]CRP data were available for 64 participants.. BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range.

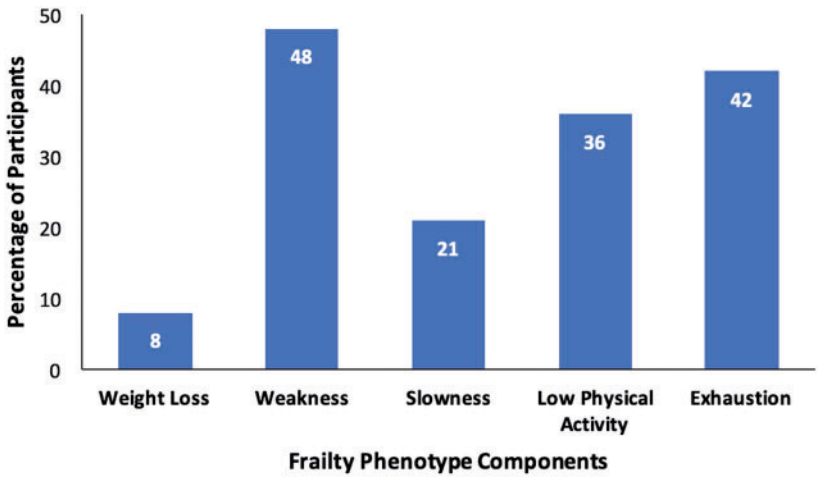

FIGURE 1: Prevalence of Frailty Phenotype components.

cut-offs suggested by the original 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 kcal/week for men and <270 kcal/week for women [1].
5. Participants were read two statements from the Center for Epidemiological Studies Depression Scale to assess self-perceived exhaustion: (i) I felt that everything I did was an effort and (ii) I could not get going [33]. Participants were then asked, 'How often did you feel this way?' and were 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 ≥2 was given for either statement [1].

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

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Table 2. SF-36 scores divided by frailty status, Frailty Phenotype 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).
*P < 0.001; . **P < 0.01;. ***P < 0.05.
SD, standard deviation; IQR, interquartile range.

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 summarize demographic and clinical characteristics 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 Frailty Phenotype score, age and CCI score. Multiple linear regression was used to assess the magnitude of the 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 SPSS statistical software (version 24; IBM, Armonk, NY, USA).

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 categorized 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 or ≥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 categorized 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 categorized 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 categorized as weak had significantly higher (worse) median scores for the question regarding health change.

Participants <65 years of age 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

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Table 3. Correlation between SF-36 domains and Frailty Phenotype score, age and CCI 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, ρ	−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 (−0.31–0.11)
Age, r	−0.05 (−0.24–0.15)	0.01 (−0.20–0.22)	0.29** (0.08–0.48)	0.17 (−0.06–0.39)	0.23*** (0.01–0.42)	0.25*** (0.02–0.46)	0.08 (−0.14–0.30)	0.22*** (0.03–0.41)
CCI score, ρ	−0.14 (−0.34–0.08)	−0.18 (−0.38–0.02)	0.06 (−0.16–0.27)	−0.09 (−0.30–0.13)	0.07 (−0.14–0.28)	−0.09 (−0.31–0.13)	−0.24*** (−0.43 to −0.04)	−0.01 (−0.23–0.21)

Data presented as correlation coefficient (95% confidence interval).
*P < 0.001; **P < 0.01; ***P < 0.05.

receiving dialysis had significantly lower scores in only 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 suggested only 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 had a significant effect on only the pain domain.

DISCUSSION

To our knowledge, this is the first study that explores the relationship between frailty, as categorized 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.* [13] and Lee *et al.* [14] have demonstrated that frailty is associated with worse HRQOL in those with CKD. However, both studies used a modified version of the Frailty Phenotype to categorize frailty, replacing objective measures of grip strength and walking speed with a self-report assessment of physical function. Such an approach has been shown to substantially overestimate 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

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Table 4. Regression analyses assessing the influence of frailty, age, gender, dialysis-dependence and comorbidity on SF-36 domains

SF-36 domain	Unstandardized β coefficient (95% CI)	Standardized 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 (−0.51–0.41)	−0.02	0.82
Female	−10.01 (−22.06–2.04)	−0.16	0.1
Dialysis	−17.49 (−30.29 to −4.69)	−0.26	0.01
CCI	−1.71 (−5.95–2.53)	−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 (0.35–1.75)	0.32	0.004
Female	9.59 (−8.75–27.94)	0.11	0.3
Dialysis	0.22 (−19.26–19.71)	0.002	0.98
CCI	2.46 (−3.99–8.92)	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 (0.10–0.82)	0.26	0.01
Female	−6.90 (−16.31–2.51)	−0.15	0.15
Dialysis	2.35 (−7.64–12.34)	0.05	0.64
CCI	−0.97 (−4.28–2.34)	−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 (0.25–1.24)	0.31	0.003
Female	−5.31 (−18.32–7.70)	−0.09	0.42
Dialysis	−0.36 (−14.17–13.46)	−0.01	0.96
CCI	−1.21 (−5.79–3.37)	−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 (−0.06–0.85)	0.18	0.09
Female	−2.02 (−13.93–9.88)	−0.04	0.74
Dialysis	−0.16 (−12.81–12.48)	−0.003	0.98
CCI	−3.82 (−8.01–0.37)	−0.18	0.07
General health (adj. $R^2 = 0.02$, $P = 0.23$)	–	–	–

Adj. R^2, adjusted R^2.

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.* [40] demonstrated that frailty was associated with worse HRQOL, symptom burden and depression scores in those with dialysis-dependent CKD. Their study used the Clinical Frailty Scale that relies upon a health care professional's assessment of frailty based upon descriptors of levels of frailty [41]. Although 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 (categorized 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 seven of the eight domains of the SF-36. Frail participants had significantly lower mean scores across five of the eight 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, the 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 emphasizing the importance of frailty screening in advanced CKD populations.

Participants categorized 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 scores. Studies within the general older population have also found that this domain has the greatest

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Table 5. Regression analyses assessing the influence of Frailty Phenotype components on SF-36 domains

SF-36 domain	Unstandardized β coefficient (95% CI)	Standardized β coefficient	P-value
Physical functioning (adj. $R^2 = 0.40$, $P < 0.001$)			
Weight loss frail	−3.55 (−24.00–16.90)	−0.03	0.73
Weakness frail	−11.89 (−23.41 to −0.37)	−0.19	0.04
Slowness frail	−12.63 (−28.04–2.79)	−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 (−32.93–33.28)	0.001	0.99
Weakness frail	−4.82 (−23.47–13.83)	−0.06	0.61
Slowness frail	−4.07 (−29.03–20.89)	−0.04	0.75
Physical activity frail	−10.38 (−28.76–8.01)	−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 (−31.53–31.01)	−0.002	0.99
Weakness frail	5.26 (−12.35–22.87)	0.06	0.55
Slowness frail	22.88 (−0.69–46.45)	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 (−13.19–13.06)	−0.001	0.99
Weakness frail	3.96 (−3.43–11.36)	0.09	0.29
Slowness frail	−4.34 (−14.23–5.55)	−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 (−22.68–10.10)	−0.08	0.45
Weakness frail	7.21 (−2.03–16.44)	0.17	0.12
Slowness frail	0.07 (−12.29–12.43)	0.001	0.99
Physical activity frail	−4.51 (−13.61–4.59)	−0.10	0.33
Exhaustion frail	−16.56 (−26.23 to −6.90)	−0.40	0.001
Social functioning (Adj. $R^2 = 0.24$, $P < 0.001$)			
Weight loss frail	10.02 (−12.89–32.93)	0.09	0.39
Weakness frail	−1.35 (−14.26–11.56)	−0.02	0.84
Slowness frail	−0.87 (−18.14–16.40)	−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 (−7.69–29.10)	0.10	0.25
Weakness frail	4.64 (−5.73–15.00)	0.08	0.38
Slowness frail	−23.57 (−37.44 to −9.71)	−0.33	0.001
Physical activity frail	−3.12 (−13.33–7.10)	−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 (−3.82–26.16)	0.16	0.14
Weakness frail	8.67 (0.23–17.12)	0.24	0.04
Slowness frail	−3.73 (−15.03–7.57)	−0.08	0.51
Physical activity frail	−4.62 (−12.94–3.70)	−0.12	0.27
Exhaustion frail	−10.36 (−19.20 to −1.52)	−0.28	0.02

Adj. R^2, adjusted R^2.

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 Impact of Fatigue on Outcomes in the Hemodialysis (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 multidimensional and multifactorial 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

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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 suggests that exercise training can improve physical function and HRQOL in frail older adults [61–63]. However, studies have not targeted patients with CKD who are pre-frail or frail, 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. First, 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. Second, 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 CKD; 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 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 article have not been published previously in whole or part, except in abstract form. Preliminary data were 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 characteristics data are the same in both articles, as data were collected from the same cohort.

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