

# Characteristics of Frailty in Haemodialysis Patients

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## Abstract

**Background:** Both frailty and cachexia increase mortality in haemodialysis (HD) patients. The clinical frailty score (CFS) is a seven-point scale and less complex than other cachexia and frailty assessments. We wished to determine the characteristics of frail HD patients using the CFS. **Methods:** Single centre cross-sectional study of HD patients completing physical activity questionnaires with bioimpedance measurements of body composition and hand grip strength (HGS). **Results:** We studied 172 HD patients. The CFS classified 54 (31.4%) as frail, who were older ( $70.4 \pm 12.2$  vs  $56.2 \pm 16.1$  years,  $p < 0.001$ ), greater modified Charlson co-morbidity (3 (2–3) versus 1.5 (0–3),  $p < 0.001$ ), and body fat (33 (25.4–40.2) versus 26.2 (15.8–34) %,  $p < 0.01$ ), but lower total energy expenditure (1720 (1574–1818) versus 1870 (1670–2194) kcal/day,  $p < 0.01$ ), lean muscle mass index (9.1 (7.7–10.1) versus 9.9 (8.9–10.8) kg/m<sup>2</sup>), and HGS (15.3 (10.3–21.9) versus 23.6 (16.7–34.4) kg), both  $p < 0.001$ . On multivariable logistic analysis, frailty was independently associated with lower active energy expenditure (odds ratio (OR) 0.98, 95% confidence limits (CL) 0.98–0.99,  $p = 0.001$ ), diabetes (OR 5.09, CL 1.06–16.66) and HGS (OR 0.92, CL 0.86–0.98). **Discussion:** Frail HD patients reported less active energy expenditure, associated with reduced muscle mass and strength. Frail patients were more likely to have greater co-morbidity, particularly diabetes. Whether physical activity programmes can improve frailty remains to be determined.

## Keywords

diseases, nursing, frailty, diabetes, obesity

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## Introduction

In Western Europe and North America an increasing number of older patients with progressive chronic kidney disease (CKD) are now being offered dialysis treatments. Thus, the demographics of the dialysis population have changed over the last decade, with increasing numbers of not only older patients, but also those with greater co-morbidity and increased dependency. As such, more patients are now being classified as having frailty (Rockwood et al. 1995), a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (Fried et al., 2001). In a recent systematic review, the prevalence of frailty was reported to range from 7% in patients with CKD stages 1–4 up to 73% in patients on

haemodialysis (HD) and was associated with increased risk of mortality and hospitalisation (Chowdhury et al., 2017).

Frailty is not only a challenge for the elderly dialysis patient and dialysis providers, as studies have reported a prevalence of frailty in 35% of HD patients younger than 65 years, and frailty was associated with a 2.6-fold increase in

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and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

**Table 1.** Clinical Frailty Scale. British Society of Geriatrics Web site.

Scale	Category	Description
1	Very fit	People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age
2	Well	People who have no active disease symptoms but are less fit than category 1
3	Managing well	People whose medical problems are well controlled, but are not regularly active beyond routine walking
4	Vulnerable	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being “slowed up”, and/or being tired during the day
5	Mildly frail	These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework
6	Moderately frail	People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing
7	Severely frail	Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months)

[www.bgs.org.uk/sites/default/files/content/attachment/2018-07-05/rockwood\\_cfs.pdf](http://www.bgs.org.uk/sites/default/files/content/attachment/2018-07-05/rockwood_cfs.pdf).

the risk of death, and an even greater chance of hospitalisation (McAdams-DeMarco et al., 2013).

In clinical practice, frailty is based on a functional assessment of patient physical ability to deal with every-day tasks. One component of frailty is muscle mass and physical strength. HD patients are reported to be at risk of pathological muscle wasting, termed sarcopenia (Cruz-Jentoft et al., 2019, Slee et al., 2020), and cachexia (Evans et al., 2008). There have been a number of definitions of cachexia (Evans et al., 2008), based on unintentional weight loss, low body mass index (BMI), along with loss of muscle mass, physical strength, fatigue, reduced appetite, and laboratory indices. Besides gender, age and ethnicity (Yoowannakul et al., 2018), some of these factors may be additionally confounded in the HD patient due to hydration status, dietary restriction and active management, including achieving haemoglobin targets (Tangvoraphonkchai & Davenport, 2018, McKeaveney et al., 2021).

We therefore wished to determine the key factors associated with frailty in HD patients, and whether these were different to those associated with cachexia.

### Patients and Methods

We reviewed body composition and muscle strength in patients with CKD established on regular outpatient HD who had measurements of active energy expenditure (AEE) based on patient self-reported physical activity (Ainsworth et al., 2013, Vilar et al., 2021, Sridharan et al., 2022). Body composition, including, skeletal lean muscle mass (SLM) and appendicular lean mass (ALM) was measured post mid-week dialysis by multifrequency segmental bio-impedance (MFBIA) (In Body S720, Seoul, South Korea), using a standardised protocol (Fürstenberg & Davenport, 2011), and indexed for height. Bioimpedance equipment was regularly serviced and calibrated and body composition had previously been validated against dual-energy X-ray absorptiometry

(Fürstenberg & Davenport, 2010; El-Katab et al., 2016). Low muscle mass was defined as an appendicular lean mass of  $<7.0 \text{ kg/m}^2$  for males and  $<5.5 \text{ kg/m}^2$  for non-Asian females and  $<5.7$  for Asian females respectively  $\text{kg/m}^2$ . Measurements of extracellular water (ECW) were indexed to total body water (TBW) and height (Davenport and Davies 2016). Patients with limb amputations and those with limb paralysis were excluded.

Muscle strength was measured using the hand grip-D strength dynamometer (HGS) (Takei Scientific Instruments Co, Nigata, Japan) (Omichi et al., 2016) and pinch gauge strength (PS) (Jamar digital plus, Lafayette Instrument, Lafayette, USA) (Jiang, Slee, & Davenport, 2021). Patients were instructed and shown how to use the hand grip and pinch gauges, and measurements were made following the manufacturer's recommendations. Patients were encouraged to make their maximal voluntary effort, and three measurements were made using their dominant arm, and the maximum strength were recorded. Two patients had an upper arm arterio-venous fistula in their dominant arm. Muscle weakness was taken as a HGS of  $<27 \text{ kg}$  for non-Asian males, and  $<28 \text{ kg}$  for Asian males, and  $<16 \text{ kg}$  for non-Asian females and  $<18 \text{ kg}$  for Asian females.

Patient frailty was assessed independently by dialysis nursing staff caring for the patient, using the 7-point Canadian clinical frailty scale (CFS) [1] (Table 1). The Charlson comorbidity score was adjusted for chronic kidney disease and age (Rattanasompattikul et al., 2012). The distress thermometer was used to determine psychological health (Maharjan & Davenport, 2020) and the social deprivation index calculated from patient's addresses using the index of multiple deprivation (IMD) (Steel et al., 2018). Routine laboratory tests [Booth et al., 2010] were obtained from the mid-week dialysis session using hospital computerised records and normalised nitrogen appearance (nPNA) and creatinine generation rates were calculated by standard methods (Salame et al., 2018; Daugirdas, 2021). Cachexia was

determined if three or more of a reduced body mass index  $<20 \text{ kg/m}^2$ , reduced muscle strength, reduced fat free muscle mass, reduced nPNA, abnormal laboratory investigations (reduced serum albumin, haemoglobin, or raised C reactive protein (CRP) were present (Evans et al., 2008).

All patients were dialysed with high flux dialysers (FX series and Fresenius 4008H dialysis machines, Fresenius Medical Company, Bad Homburg, Germany) (Tangvoraphonkchai et al., 2018), with ultra-pure quality dialysis water and anticoagulated with a single bolus dose of tinzaparin (Leo Laboratories, Princes Risborough, UK), median dose 2500 (2500–2500) IU (Davenport, 2013).

### Statistical Analysis

Results are expressed as mean  $\pm$  standard deviation, or median and interquartile range, or percentage. Data was analysed using the D'Agostino and Pearson normality test, and numerical data was analysed by t test if normally distributed and non-parametric data by Mann Whitney U test. Categorical data was analysed using the Chi square test. Cohen's kappa statistic was used to compare frailty and cachexia groupings. Appropriate corrections for small numbers and multiple testing, were applied. Univariate analysis was by Pearson and Spearman analysis, respectively. A logistic step-backward model for frailty included all variables with univariate association  $p < 0.1$ . Variables were then retained if statistically significant, or improved model fit. Statistical analysis was performed using Graph Pad Prism (version 9.0, Graph Pad, San Diego, CA, USA), Statistical Package for Social Science version 26.0 (IBM Corporation, Armonk, New York, USA), and Analyse-It (version 4.0, Leeds, UK). Statistical significance was taken at or below the 5% level.

### Ethics

Patients in this study provided informed consent in keeping with the Helsinki declaration, and the study was reviewed and approved by a national ethics committee system

### Results

We studied 172 patients recruited from a single centre for a study estimating energy expenditure, who had contemporaneous bioimpedance and HGS and PS measurements (Table 2). Patients were divided according to the CFS scale, with frailty defined as a score of five or greater (Rockwood et al., 2005). Frail patients were older, with greater co-morbidity scores and more likely to have diabetes. However, HD adequacy was similar with equivalent urea clearance, and if anything, serum  $\beta_2$  microglobulin, a marker of middle molecule clearance, was lower. Frail patients had lower lean total body muscle and appendicular muscle (Figure 1) (Cawthon et al., 2014), and lower HGS and PS (Figure 2). However, BMI was greater in frail patients, with greater fat mass (Table 3). Resting energy

expenditure (REE) was similar, but frail patients had lower total energy expenditure (TEE), when active energy expenditure (AEE) was added to REE. Serum creatinine, and normalised creatinine generation rates were lower in frail patients, although normalised nitrogen protein accumulation was similar. CRP was higher in frail patients. Serum cholesterol was lower in frail patients, but more had been prescribed 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins). In terms of markers of volume overload, N terminal pro-brain natriuretic peptide (NTproBNP) was similar and although the ratio of ECW/TBW was greater, ECW adjusted for height was also similar.

On univariate analysis a number of factors were associated with CFS scores (Table 4). We then constructed a multivariable logistic model, and only diabetes was independently associated with frailty, along with lower physical activity as assessed by AEE and muscle weakness measured by HGS (Table 5).

There have been several definitions of cachexia. The Evans criteria include a BMI of  $<20$  or a designated weight loss (Evans et al., 2008), and we found no difference in these major criteria between frail (31.5%) and non-frail patients (33.1%). There were differences in some minor laboratory criteria notably more frail patients having a raised CRP (55.5 vs. 38.1%,  $X^2=4.6$ ,  $p = 0.033$ ), though there were no differences in the proportions with low albumin (1.9vs 3.4%) and low haemoglobin (72.2 vs 77.9%) levels. When considering cut-offs used to define sarcopenia, more frail patients had both loss of muscle (45.3 vs. 25.9%,  $X^2=4.0$ ,  $p = 0.047$ ), and HGS weakness (71.7 vs 44.7%  $X^2=12.1$ ,  $p < 0.001$ ) (Evans et al., 2008; Cruz-Jentoft et al., 2019,,7). Comparing frailty and cachexia using the CFS and Evans criteria, the kappa coefficient was 0.14 ( $-0.02$ – $0.29$ ), suggesting only slight agreement between the two scales.

### Discussion

Both frailty and cachexia are associated with increased risk for mortality [Fried et al., 2001; Evans et al., 2008; McAdams-DeMarco et al., 2013; Cruz-Jentoft et al., 2019]. The CFS, a seven-point scale of physical activity (Rockwood et al., 2005), can be readily applied in clinical practice. We wished to review the phenotype of frailty using the CFS. Frail patients were older, had greater co-morbidity, particularly diabetes, less physical energy expenditure, with lower muscle mass, and less upper body strength, and a raised CRP. They also had a higher BMI due to a greater fat mass.

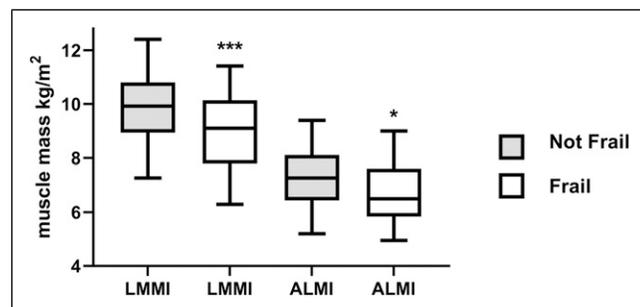
#### Muscle Mass and Hand Grip Strength

A number of definitions of cachexia have been introduced to differentiate physiologic age-related muscle loss from pathological loss (Evans et al., 2008; Cawthon et al., 2014; Cruz-Jentoft et al., 2019). CKD patients are at greater risk of loss of muscle mass (Fahal, 2014). Around a quarter of our non-frail patients had lower muscle mass, and depending on which cut

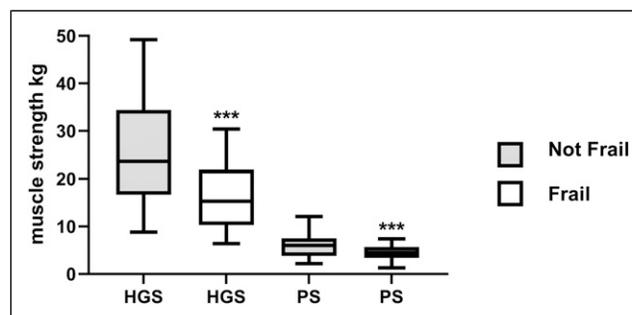
**Table 2.** Patient demographics, and dialysis treatment.

Variable	All Patients	Not Frail	Frail
Number	172	118	54
Male/female	113/59	83/35	30/24
Age years	60.2 ± 16.5	56.2 ± 16.1	70.4 ± 12.2***
Diabetic (%)	58 (33.7)	29 (24.6)	29 (53.7) ***
White/Asian/African	84/40/48	53/30/35	31/10/13
Charlson comorbidity	2.0 (1.0–3.0)	1.5 (0–3.0)	3.0 (2.0–3.0)***
Distress thermometer	2.0 (0–5)	1.0 (0–5)	3.5 (0–5.5)
Social deprivation index	11777 (6, 083–20, 306)	12166 (62, 31–205, 05)	10530 (60, 85–187, 25)
Primary renal disease	—	—	—
glomerulonephritis	32 (18.6%)	26 (22.0%)	6 (11.1%)
hypertension/Ischaemia	31 (18.0%)	20 (16.9%)	11 (20.4%)
diabetes	44 (25.6%)	23 (19.5%)	21 (41.2%)*
dysplastic/Congenital	20 (11.6%)	18 (15.3%)	2 (3.7%)
interstitial	17 (9.9%)	15 (12.7%)	2 (3.7%)
vasculitis/SLE	5 (2.9%)	3 (2.5%)	2 (3.7%)
other/Unclassified	20 (11.6%)	13 (11.0%)	7 (13.0%)
Vintage months	33.7 (17.2–70.8)	33.6 (17.2–69.6)	33.8 (19.9–66.5)
Dialysis session hrs	3 (3–3)	3 (3–3)	3 (3–3)
Dialysis sessions/wk	3.8 ± 0.5	3.8 ± 0.6	3.8 ± 0.4
Dialyser size m <sup>2</sup>	2.2 (1.8–2.2)	2.2 (1.8–2.2)	1.8 (1.8–2.2)*
Fistula/graft/CVC	135/7/30	92/5/21	32/2/9
Pre HD SBP mmHg	142 ± 25	141 ± 23	145 ± 29
Antihypertensives	1 (0–2)	1 (0–2)	1 (0–1)
Weight kg	70.3 ± 17.0	69.7 ± 16.6	71.5 ± 17.9
Weight change 6 mo	−0.4 (−3.2 to 2.1)	−0.2 (−3.1 to 2.1)	−0.7 (−3.7 to 1.6)
Weight change 12 mo	−1.5 (−5.2–2.1)	−1.4 (−4.9 to 2.1)	−1.9 (−6.3 to 2.3)
Urea reduction ratio %	74.7 ± 7.7	74.6 ± 7.7	75.0 ± 7.8
Dialysis eKt/V	1.43 ± 0.3	1.43 ± 0.29	1.45 ± 0.34
β2 microglobulin mg/L	27.6 (23.8–31.4)	28.3 (24.3–32.1)	26.2 (21.5–30.3)**

Systemic lupus erythematosus (SLE), duration of dialysis treatment (vintage), central venous catheter (CVC), number of antihypertensive medications (antihypertensives), haemodialysis (HD), systolic blood pressure (SBP), equilibrated dialysis session urea clearance (eKt/V). Charlson co-morbidity adjusted for chronic kidney disease and age factors. Values expressed as integer, mean ± standard deviation, median (interquartile range). \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  non-frail versus frail.



**Figure 1.** Skeletal lean muscle mass index (SMMI) and appendicular lean mass index (ALMI) in frail patients (CFS score >4) and not-frail patients (CFS score ≤4). Box plots, median, quartiles and 10 and 90% confidence limits. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .



**Figure 2.** Hand grip strength (HGS) and pinch strain gauge (PS) in frail patients (CFS score >4) and not-frail patients (CFS score ≤4). Box plots, median, quartiles and 10 and 90% confidence limits. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ .

off values were used then 34 and 7.6% of this group had moderate and severe muscle loss (Cawthon et al., 2014), Proportionally more patients had lower HGS, with approximately 77% of frail and 42% of non-frail patients with

reduced upper body strength. Previous reports have suggested that muscle mass and strength may vary with patient ethnicity (Yoowannakul et al., 2018; Jiang, Singh Maharjan, et al., 2021), but in this study we found no effect of gender or

**Table 3.** Body composition, energy expenditure, laboratory investigations and bioimpedance assessment of volume status.

Variable	All Patients	Not Frail	Frail
Body mass index kg/m <sup>2</sup>	25.2 ± 5.8	24.5 ± 5.2	26.6 ± 7.9*
Fat mass kg	18.2 (11.8–27.7)	16.9 (9.4–24.4)	22.6 (15.6–31.3)**
% Body fat	29.2 (19.2–36.1)	26.2 (15.8–34.6)	33.0 (25.4–40.2)**
REE kcal/day	1588 (1455–1721)	1590 (1464–1729)	1575 (1450–1691)
TEE kcal/day	1745 (1460–1745)	1870 (1670–2194)	1720 (1574–1818)**
AEE kcal/day	297 (253–401)	321 (275–507)	256 (206–287)
nPNA g/kg/day	1.20 ± 0.39	1.21 ± 0.39	1.18 ± 0.40
nCreatGen mg/kg/day	16.6 (13.1–20.6)	17.3 (14.0–21.7)	15.3 (11.7–19.3)*
Haemoglobin g/L	110.8 ± 13.7	111.4 ± 14.4	109.5 ± 12.0
Darbopoietin ug/week	40 (20–60)	40 (20–60)	40 (15–70)
ERI iu/kg/gHb/wk	1.04 (0.55–1.77)	1.08 (0.6–1.59)	0.95 (0.38–2.04)
Sodium mmol/L	139.4 ± 1.3	139.6 ± 1.3	138.8 ± 2.8
Potassium mmol/L	5.1 ± 0.7	5.2 ± 0.7	4.9 ± 0.8
Bicarbonate mmol/L	21.2 ± 2.8	21.0 ± 2.5	21.6 ± 3.3
Urea mmol/L	19.9 ± 6.2	20.1 ± 6.4	19.6 ± 6.3
Creatinine umol/L	765 (602–966)	822 (655–1024)	679 (559–815)***
Albumin g/L	40.6 ± 5.1	41.3 ± 5.2	39.1 ± 4.5
Cholesterol mmol/L	3.92 ± 1.2	4.1 ± 1.3	3.6 ± 1.1*
Statin prescription %	51.1	45.5	72.6 **
Calcium mmol/L	2.30 ± 0.16	2.30 ± 0.16	2.32 ± 1.5
Phosphate mmol/L	1.80 ± 0.56	1.84 ± 0.59	1.70 ± 0.49
C Reactive protein mg/L	4.0 (1.0–11.0)	3.0 (1.0–9.0)	6.0 (2.0–12.0)*
Glucose mmol/L	6.7 (5.4–8.3)	6.1 (5.2–7.7)	7.6 (6.3–8.4)
NTproBNP pg/mL	3217 (13, 48–117, 99)	3799 (11, 63–108, 78)	3217 (14, 35–117, 99)
ECW/TBW ratio	0.396 ± 0.019	0.388 ± 0.015	0.401 ± 0.016***
ECW/height L/m	5.12 ± 0.83	5.15 ± 0.75	5.0 ± 0.99

Resting energy expenditure (REE), total energy expenditure (TEE), active energy expenditure (AEE), normalised protein nitrogen generation (nPNA), normalised creatinine generation rate (nPcreatGen), erythropoietin resistance index (ERI), prescription of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statin), N terminal pro-brain natriuretic peptide (NTproBNP), extracellular water (ECW), total body water (TBW). \*  $p < 0.05$ , \*\*  $p < 0.01$  \*\*\*  $p < 0.001$  non-frail versus frail.

ethnicity. Previous studies have also observed that dialysis patients have lower muscle strength compared to muscle mass. Although this may be due to changes in muscle composition and muscle energetics [29], as muscle contains 90% water, then measurements of muscle mass are affected by hydration status (Panorchan et al., 2015).

### Physical Activity

Some definitions of cachexia, and sarcopenia include measurement of physical activity, such as gait speed, or sit to stand (Evans et al., 2008; Cruz-Jentoft et al., 2019; McKeaveney et al., 2021). However, these timed tests may be confounded in dialysis patients due to mineral bone disease and impracticable for the increasing number of wheelchair-bound dialysis patients. We measured self-reported energy expenditure, and although there was no difference in REE, however overall TEE was lower in frail patients, when active energy expenditure was determined. Other studies have used the Fatigue questionnaire (FACIT-F) (McKeaveney et al., 2021), a 40-item measure that assesses self-reported fatigue

and its impact upon daily activities and function. However, the results of this questionnaire can be confounded by fatigue secondary to anaemia and volume overload (Yoowannakul et al., 2021), and psychological distress. In our cohort distress thermometer scores were similar for both frail and non-frail patients, and previous studies have not shown an effect of psychological distress on muscle strength in dialysis patients (Camilleri et al., 2017).

### Weight Change

Other criteria for diagnosing cachexia have included weight loss (Yoowannakul et al., 2018). However, we did not observe a significant difference in weight loss between frail and non-frail patients, although 20.4% of frail patients had lost more than 5% of body weight over the previous 6 months compared to 13.6% of non-frail patients. Compared to the normal geriatric population, episodes of intercurrent illness, or reduction in hydration status in dialysis patients may have confounded changes in weight. Overall weight was not different between frail and non-frail patients. Indeed, BMI

**Table 4.** Univariate associations with clinical frailty score.

Variable	r	p Value
Age	0.51	<0.001
Extra cellular water/Total body water	0.47	<0.001
Charlson comorbidity score	0.46	<0.001
Hand grip strength	-0.43	<0.001
Total energy expenditure	-0.40	<0.001
Normalised creatinine generation rate	-0.38	<0.001
Serum creatinine	-0.38	<0.001
Pinch strength	-0.37	<0.001
Active energy expenditure	-0.36	<0.001
Intracellular water	0.33	<0.001
% Body fat	0.31	<0.001
Serum albumin	-0.30	<0.001
Lean muscle index	-0.29	<0.001
Resting energy expenditure	-0.29	0.0013
Total body water	-0.27	0.003
Apppendicular lean mass index	-0.22	0.0054
C Reactive protein	0.22	0.0034
Serum cholesterol	-0.20	0.0092
Body fat mass	0.23	0.0025
Extracellular water	-0.18	0.0187
Gender (male)	-0.18	0.0195
Dialysis session time	-0.18	0.0161
Dialyser surface area	-0.19	0.0172
Serum $\beta$ 2 microglobulin	-0.177	0.0208
Blood pump speed	-0.17	0.032
Serum potassium	-0.19	0.0172
Serum sodium	-0.16	0.496

**Table 5.** Logistic regression model of factors indecently associated with frailty.

Variable	$\beta$	StE $\beta$	Wald	Odds Ratio	95% CL	p
AEE	-0.011	0.003	10.14	0.98	0.98-0.99	0.001
Diabetes	1.63	0.57	8.07	5.09	1.06-16.66	0.004
HGS	-0.08	0.034	5.62	0.92	0.86-0.98	0.018

Active energy expenditure (AEE), hand grip strength (HGS). Standard error  $\beta$  (StE  $\beta$ ), 95% confidence limits (95% CL). Nagelkerke  $r^2=0.47$ .

was higher due to an increase in body fat. Previous reports have introduced the term of sarcopenic obesity to describe patients with loss of muscle mass, but with gain of fat weight (Malhotra et al., 2017).

### Standard Laboratory Investigations

Similarly, laboratory criteria have been suggested to support a diagnosis of cachexia. As anaemia is commonly observed in dialysis patients, taking a haemoglobin cut point of 120 g/L (Yoowannakul et al., 2018), did not differentiate frail from non-frail patients. There was also no difference adjusting the weekly dose of erythropoietin stimulating agent (ESA) for

haemoglobin and body weight. Again, when using a pre-dialysis serum albumin cut point of 38 g/L, there were no differences between frail and not-frail groups. However, more than half the frail patients had a CRP of >5 mg/L., highlighting the over-lap between cachexia, protein energy wasting (PEW) and frailty (Hanna et al., 2020). Although cholesterol concentrations were lower in the frail patients, more frail patients were prescribed statins, so making interpretation unreliable.

### Estimates of Dietary Protein Intake And Dialysis Adequacy

Dialysis patients have a restricted diet (Uribarri, 2018), and reduced protein intake has been highlighted as a risk factor for PEW and cachexia (Hanna et al., 2020). We calculated dietary protein intake based on changes in urea with dialysis (Kalantar-Zadeh, Supasyndh, Lehn, McAllister, & Kopple, 2003), and nPNA did not differ with frailty. Frail patients did not live in more socially deprived areas (Steel et al., 2018). Dialysis adequacy as assessed by dialyser urea clearance (eKt/V) was similar, although  $\beta$ 2 microglobulin, a surrogate for middle molecule clearance, was lower in the frail patients. Daugirdas recently introduced the creatinine generation rate (Daugirdas, 2021). So, although nPNA was similar, frail patients had both lower serum creatinine values, and lower creatinine generation rates, in keeping with lower muscle mass and less physical activity.

### Study Confounders

As with any observational study, there are a number of considerations. Patient physical activity was self-reported using validated questionnaires (Ainsworth et al., 2011; Vilar et al., 2020; Sridharan et al., 2022). The frailty CFS scores were assessed by the dialysis nursing staff, who were blinded to bioimpedance and muscle strength measurements. The research team calculating energy expenditure were independent of the team administering the activity questionnaires, and both were blinded to the CFS. Bioimpedance measurements can be affected by hydration status (Panorchan et al., 2015). As, such all measurements were standardised to post mid-week dialysis session. Although the ECW/TBW ratios were greater for the frail group, an increased ratio can also be due to a reduced ICW, and loss of cell mass (Davenport and Davies 2014; Tangvoraphonkchai & Davenport, 2018). Adjustment of ECW to body height and NTproBNP were similar for both frail and non-frail groups, suggesting similar hydration status. We did not formerly assess dietary intake, but used nPNA as a surrogate of dietary protein intake.

### Summary

In summary, we found that the CFS, a seven-point scale of patient function identified a group of dialysis patients with

reduced physical activity with lower active energy expenditure, muscle mass, muscle strength and lower creatinine generation. Frail patients had greater co-morbidity, in particular diabetes, less physical activity and muscle weakness. Whether increasing physical activity levels will improve frailty scores and reduce the increased risk of mortality associated with frailty will require prospective studies.

### Author Contributions

KF conceived the study, edited versions of paper  
 SS obtained study approvals, analysed data, edited versions of paper  
 HH collected data, edited versions of paper  
 AD conceived study, analysed data, edited versions of paper  
 All authors approved the final version

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### Ethical Approval

The study was reviewed and approved by the United Kingdom (UK) national ethics committee system 15/LO/0315.

### Data Availability

Anonymised data available on request. The anonymised data underlying this article will be shared on reasonable request to the corresponding author. The data contained in this paper has not been published in whole or part form Characteristics of frailty in haemodialysis patients: muscle mass, hand grip strength and energy expenditure.

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