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ORIGINAL ARTICLE

Investigating the relationship between **FR**ailty **A**nd Quality of L**I**fe in patients with heart fai**L**ure and CKD (FRAIL study)

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Abstract

Aims Patients with chronic kidney disease (CKD) or heart failure (HF) are disproportionally affected by frailty, an independent predictor of morbidity. The prevalence of frailty and its impact on quality of life (QoL) in a unique population of patients with both CKD and HF (CKD-HF) is unclear. The aim of this study was to investigate the association between frailty and QoL in patients with CKD-HF.

Methods and results Patients were identified from a tertiary care cardiorenal clinic. Eligible patients had CKD-HF with a stable estimated glomerular filtration rate of $<$60 mL/min/1.73^2. Data were collected from each participant at one point in time using surveys delivered by study personnel between 14 July 2022 and 31 March 2023. Frailty was defined as Modified Frailty Phenotype (MFP) score $\geq$3. The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) was used to assess QoL. Demographic data were retrospectively collected from electronic patient records. Demographics and QoL were compared between frail and non-frail cohorts using Pearson's *R* and Student's *t*-test (two-tailed, alpha-priori = 0.05). One hundred five participants consented, and 103 completed the questionnaires in full. Amongst the 103 participants, 49.5% (n = 51) were frail. Frailty was related to sex (P = 0.021) and medication count (P = 0.007), however not to other clinical measures, including estimated glomerular filtration rate (P = 0.437) and ejection fraction (P = 0.911). Frail patients reported poorer QoL across physical functioning ($P < 0.001$), general health ($P < 0.001$), bodily pain (P = 0.004), social functioning ($P < 0.001$), and energy levels ($P < 0.001$), however not emotional wellbeing (P = 0.058); 51.5% cited 'better quality of life' as their healthcare priority, over longer survival (23.3%) or avoiding hospital admissions (22.3%). This was consistent across frail and non-frail groups.

Conclusions A large proportion of CKD-HF patients are frail, regardless of disease severity, and more susceptible to significantly poorer QoL across physical and social domains. Improving QoL is the priority of patients across both frail and non-frail cohorts, further emphasizing the need for prompt recognition of frailty as well as possible intervention and prevention.

Keywords Chronic kidney failure; Frailty; Heart failure; Observational; Quality of life

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Introduction

Both chronic kidney disease (CKD) and heart failure (HF) are lifelong, progressive conditions with a significant disease burden worldwide.[1,2] An increasing number of patients with CKD have concomitant HF (CKD-HF), and vice versa. The physiological relationship between these two diseases is complex and bidirectional, with each increasing the risk of developing the other.[3,4] Furthermore, the management of patients with CKD-HF is challenging as concerns due to worsening renal function and hyperkalaemia often preclude the use of evidence-based HF medication.[5] In response to this, our

tertiary centre has established a novel dedicated CKD-HF inter-disciplinary clinic with input from both cardiologists and nephrologists to manage these complex clinical situations.[5]

Frailty is a term which describes cumulative decline in multiple physiological domains, causing a dynamic state of increased vulnerability to stressors (clinical or non-clinical).[6–10] Individuals with frailty may experience a disproportionate reaction to a stressor, which may be insignificant in a healthy individual (e.g. increased risk of hospitalization or death, from a minor infection or introduction of a new medication).[10] Frailty has garnered increasing interest over recent years due its association with mortality, disability, falls and long-term care.[6] Although not synonymous, the incidence of frailty is more common and seen at an earlier age in patients with multiple co-morbidities.[8,11]

Individuals with CKD or HF suffer frailty more frequently than both the general population and individuals with other chronic medical conditions.[12–14] Estimates of frailty amongst CKD patients vary depending on renal function; previous studies have found rates of 7% in a population with mean eGFR 49 mL/min/1.73^2,[15] 43% with mean eGFR 26.8 mL/min/1.73^2,[16] and 60% in dialysis dependent populations.[13,14] Frailty amongst HF populations ranges from 15% to 74% depending on the study population and methodology used.[10,17,18] Comparatively, rates of frailty in community populations living without CKD or HF are lower at 11%.[19] To the authors knowledge, no previous study has investigated the prevalence of frailty in patients with both CKD-HF.

Health-related quality of life (HR-QOL) is a widely used, validated measure of how an individual perceives their physical and mental health, and how their health impacts their quality of life.[11,20] In patients with CKD or HF, HR-QOL scores tend to worsen with increasing disease severity[21–23]; however, this has not previously been studied in patients with both CKD-HF.

The association between frailty and HR-QOL is complex and research investigating the relationship between them is limited. Previous studies have highlighted the importance of identifying frailty and poor HR-QOL early, and the necessity for targeted interventions aimed at specific characteristics of frailty in order to optimize HR-QOL.[16,24–27] However, these studies have been limited in small populations and have considered patients living with either CKD or HF, not both.

Furthermore, patients with CKD-HF are often multimorbid and polypharmacy is common.[5] Previous studies have identified a positive relationship between polypharmacy and frailty[9,28]; however, no previous study has considered this relationship within a sample of CKD-HF patients. This is important as recent years have seen the expansion of evidence-based therapies for HF with reduced ejection fraction (EF), and patients are now recommended to take at least four drugs.[29] The primary endpoint of these landmark trials on which these recommendations are based were predominantly mortality or hospital admissions.[29] However, the majority did not consider frailty status as an outcome. We hoped that this study would help us to improve our understanding of the relationship between frailty and polypharmacy in CKD-HF patients. Furthermore, we wanted to learn about the healthcare priorities of patients with CKD-HF, to better enable patient specific needs to be met in trials and clinical practice.

To our knowledge, no study has yet investigated the relationship between frailty and HR-QOL in patients with CKD-HF. Whilst evidence specific to this population is limited, there is unanimous agreement that both HR-QOL and frailty are important outcomes in the management of both CKD and HF. Furthermore, their early assessment can provide important insights to guide the management for the unique challenges faced by this population.

The primary aim of this study was to investigate the impact of frailty on HR-QOL in patients with both CKD-HF. Objectives included (i) assessing the prevalence of frailty in this patient cohort of CKD-HF; (ii) assessing the impact of frailty on HR-QOL in CKD-HF; (iii) assessing the relationship between frailty and HR-QOL with clinical status, polypharmacy, demographics in patients with CKD-HF; (iv) assessing patient priorities within healthcare planning.

Methods

Study design

This study used an observational cross-sectional questionnaire, with a convenience sampling method. This was a single centre study that took place within a CKD-HF inter-disciplinary clinic in a tertiary university teaching hospital in London, England between 14 July 2022 and 31 March 2023. The study adhered to the Declaration of Helsinki and was approved by the Cambridge East Research Ethics Committee (REC) and approved by HRA (IRAS:294629).

All potentially eligible patients were informed about the study via a written participant information sheet (PIS) distributed via post, email or in person when they attended for a joint cardiorenal clinic appointment. This was followed up with a telephone call. If they wished to provide their informed consent following discussion, patients were offered to complete the questionnaire over the telephone, or to complete the questionnaire online using a secure online survey platform.[30]

The inclusion and exclusion criteria for participants can be found in *Table 1*.

Outcomes

Frailty instrument

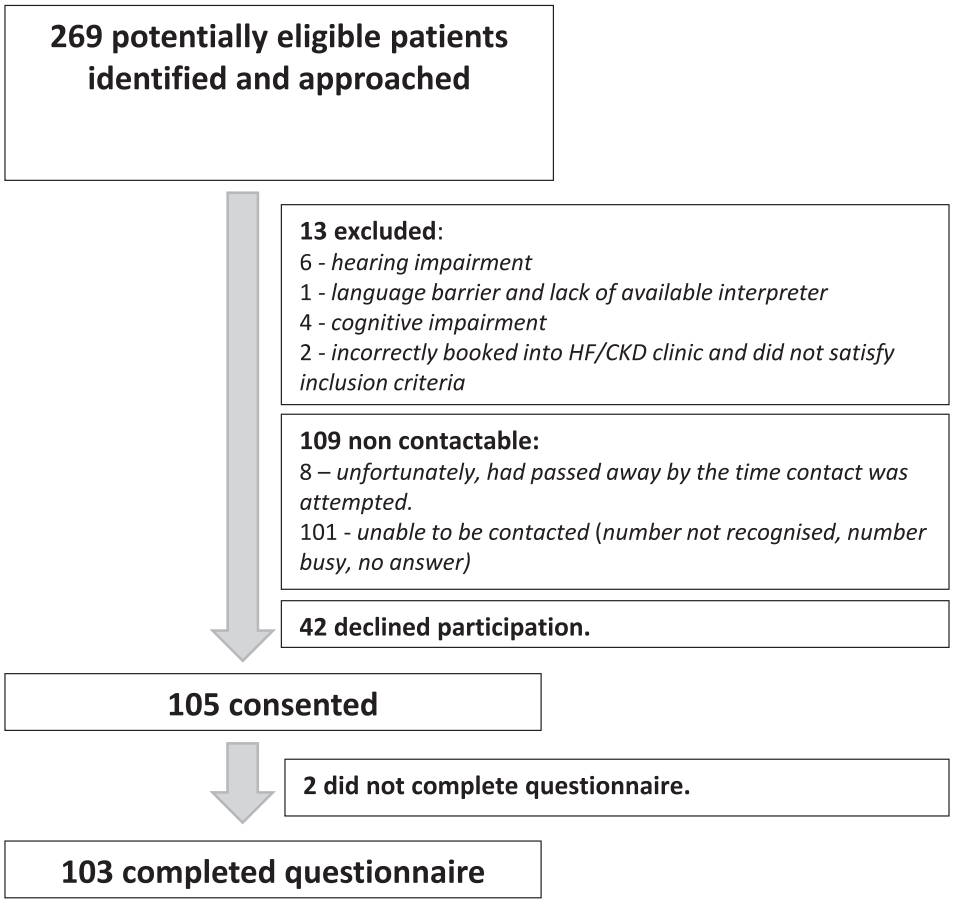
Frailty was assessed and quantified using both the 'Clinical Frailty Scale (CFS)' and the 'Modified Frailty Phenotype

Table 1 Inclusion and exclusion criteria

Inclusion criteria:
1 Diagnosis of CKD stages three to five
2 Ability to provide informed verbal consent
3 Attending St George's Hospital joint heart failure and chronic kidney disease clinic, to which referrals were only accepted provided patients met contemporary diagnostic criteria for each condition. The clinic used the most recent NICE guideline for diagnosis of HF [NG 106, 1.2]
4 Aged 18 or over
Exclusion criteria:
1 Communication barriers (e.g. hard of hearing and language barrier where no interpreter available)
2 Cognitive impairment. Cognitive impairment was assessed by the responsible clinician. If deemed necessary, a formal mental health state assessment was performed using the Abbreviated Mental Test-10 validated mental impairment examination. Patients scoring 3 out of 10 or less (in keeping with severe cognitive impairment) were excluded as the validity of the SF-36 questionnaire is adversely affected.

CKD, chronic kidney disease; HF, heart failure; NICE, National Institute for Health and Care Excellence; SF-36, 36-item Short Form Survey Instrument.

Figure 1 Recruitment flow chart.



(MFP)', which are both validated and used widely in clinical practice and research, including in HF and CKD, although are not specifically validated for these populations.[10,14,31–36] Both were deemed appropriate as they are simple and easy to use both over the telephone or within an online survey. The MFP constitutes four domains: slowness/weakness, exhaustion, physical inactivity and unintentional weight loss. Frailty is defined as a score equal to or greater than three. The CFS is a frailty tool ranging from 1 (*very fit*) to 9 (*terminally ill*), and constitutes assessment of several domains including cognition, function, and co-morbidities. For the purposes of our analysis, MFP was deemed to be more appropriate and truly representative of frailty, as opposed to the CFS which also constitutes co-morbidities which are common in patients

with HF-CKD. Thus, the analyses were conducted as patients that were deemed frail according to MFP, vs those that were not.

HR-QOL instrument

The Medical Outcomes Study 36-item Short Form Health Survey (SF-36) tool was used to measure HR-QOL. The SF-36 is a publicly available, validated tool for assessing HR-QOL and is used widely across research and clinical specialties.[37–40] The SF-36 provides an objective assessment of the following eight domains: physical functioning, role limitation due to physical functioning, role limitations due to emotional functioning, energy/fatigue, emotional well-being, social functioning, pain and general health. In SF-36, scores range from zero (*worst possible health state*) to 100 (*best possible health state*). The SF-36 was selected as the tool for this study due to the ease with which it can be carried out over the phone, the objective nature of the questions and low inter-observer variability.[38–40]

At the time that both questionnaires were completed, patients were asked to rank the following in terms of their healthcare priorities: (i) longer survival, (ii) better quality of life, or (iii) avoiding hospital admissions.

Demographic data

Participants' demographic data were collected retrospectively from electronic patient records including age, ethnicity, smoking history, BMI, number of regular medications, eGFR, EF, creatinine levels and albumin: creatinine ratio.

Statistical analysis

Sample size was calculated based on the prevalence of frailty. As patients with CKD have a frailty prevalence of approximately 40–60%,[12–14,16] and frailty in HF populations ranges from 15% to 74%,[17,18] a sample size of between 100 and 120 was considered appropriate to estimate a prevalence of 60–80% with a precision of 8–10%. Data were analysed and graphs were created using R 4.3.0 with ggplot2 and ggpubr[41] package. Descriptive statistics were used to describe baseline characteristics of participants.

Continuous variables were analysed with Shapiro–Wilk test to determine normality. Parametric variables were compared between frail and non-frail patients using independent sample *t*-test. Non-parametric continuous variables were compared using Mann–Whitney *U* test, and categorical variables were compared using chi-squared test. Bivariate correlations between continuous variables were calculated using Pearson's correlation coefficient (*R*). *P*-values were two-tailed and considered significant if <0.05.

Results

A total of 269 patients were identified as potentially eligible for the study and were approached. Thirteen were excluded

Table 2 Baseline characteristics of participants by frailty status

Baseline characteristics				
MFP	Overall	No	Yes	
n	103	52	51	*P*-value
Age, median [IQR]	76.00 [68.50, 82.00]	78.50 [69.75, 82.25]	76.00 [67.50, 80.00]	0.503
Male, No. (%)	64 (62.1)	38 (73.1)	26 (51.0)	0.021
Ethnicity, No. (%)				0.079
Asian	24 (23.3)	8 (15.4)	16 (31.4)	
Black	10 (9.7)	3 (5.8)	7 (13.7)	
Mixed	2 (1.9)	2 (3.8)	0 (0.0)	
Other	10 (9.7)	5 (9.6)	5 (9.8)	
White	57 (55.3)	34 (65.4)	23 (45.1)	
BMI, mean (SD)	28.65 (6.26)	27.53 (5.68)	29.76 (6.66)	0.083
Smoking, No. (%)				0.749
Ex	53 (51.5)	29 (55.8)	24 (47.1)	
Never	41 (39.8)	18 (34.6)	23 (45.1)	
Smoker	7 (6.8)	4 (7.7)	3 (5.9)	
Unknown	2 (1.9)	1 (1.9)	1 (2.0)	
CKD stage, No. (%)				0.758
CKD Stage 3	55 (53.4)	29 (55.8)	26 (25.2)	
CKD Stage 4	38 (36.9)	19 (36.5)	19 (37.3)	
CKD Stage 5	10 (9.7)	4 (7.7)	6 (11.8)	
Ejection fraction, median (IQR)	42.50 [32.00, 52.00]	38.50 [32.38, 49.00]	42.50 [32.00, 53.50	0.911
eGFR, mean (SD)	29.34 (11.43)	30.21 (11.30)	28.45 (11.62)	0.437
Medication count, mean (SD)	9.81 (3.4)	8.92 (3.55)	10.71 (3.0)	0.007

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MFP, modified frailty phenotype; SD, standard deviation.

Figure 2 Graphs representing the relationship between frailty and several parameters of HR-QOL: energy, general health, physical functioning, social functioning, bodily pain, and mental health.

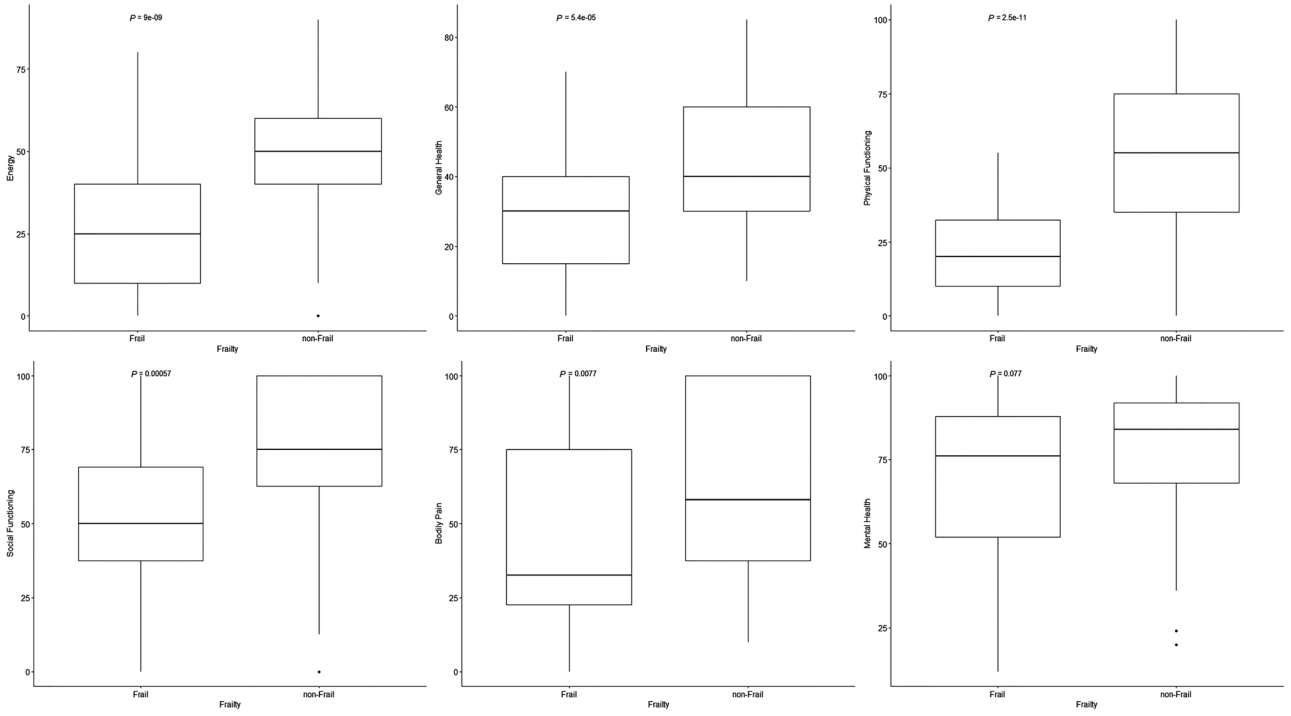


Table 3 Patient priorities and Quality of Life parameter results by frailty status

MFP *N*	Overall 103	No 52	Yes 51	*P*-value
First priority (%)				0.208
Longer survival	24 (23.3)	15 (28.8)	9 (17.6)	
Better quality of life	53 (51.5)	26 (50.0)	27 (52.9)	
Reduced hospital admission	23 (22.3)	11 (21.2)	12 (23.5)	
Not sure	3 (2.9)	0 (0.0)	3 (5.9)	
Second priority (%)				0.637
Longer survival	39 (37.9)	22 (42.3)	17 (33.3)	
Better quality of life	33 (32.0)	16 (30.8)	17 (33.3)	
Reduced hospital admission	27 (26.2)	13 (25.0)	14 (27.5)	
Not sure	4 (3.9)	1 (1.9)	3 (5.9)	
Third priority (%)				0.119
Longer survival	36 (35.0)	14 (26.9)	22 (43.1)	
Better quality of life	14 (13.6)	10 (19.2)	4 (7.8)	
Reduced hospital admission	49 (47.6)	27 (51.9)	22 (43.1)	
Not sure	4 (3.9)	1 (1.9)	3 (5.9)	
Clinical Frailty Scale (CFS), mean (SD)	4.79 (1.54)	3.83 (1.32)	5.76 (1.07)	<0.001
Frailty CFS (%)	81 (78.6)	30 (57.7)	51 (100.0)	<0.001
Moderate or severe frailty on CFS (%)	39 (37.9)	6 (11.5)	33 (64.7)	<0.001
Physical functioning, median [IQR]	35.00 [15.00, 55.00]	55.00 [35.00, 75.00]	20.00 [10.00, 32.50]	<0.001
Role limitations due to physical health, median [IQR]	0.00 [0.00, 50.00]	25.00 [0.00, 75.00]	0.00 [0.00, 25.00]	<0.001
Emotional well-being, median [IQR]	80.00 [60.00, 92.00]	84.00 [68.00, 92.00]	76.00 [52.00, 88.00]	0.121
Role limitations due to emotional problems, median [IQR]	100.00 [33.33, 100.00]	100.00 [66.67, 100.00]	66.67 [16.50, 100.00]	0.058
Energy/fatigue, median [IQR]	40.00 [20.00, 50.00]	50.00 [40.00, 60.00]	25.00 [10.00, 40.00]	<0.001
Social functioning, median [IQR]	62.50 [37.50, 100.00]	75.00 [62.50, 100.00]	50.00 [37.50, 69.00]	<0.001
Pain, median [IQR]	47.50 [23.00, 90.00]	58.00 [37.50, 100.00]	32.50 [22.50, 75.00]	0.004
General health, median [IQR]	35.00 [20.00, 50.00]	40.00 [30.00, 60.00]	30.00 [15.00, 40.00]	<0.001

IQR, interquartile range; MFP, Modified Frailty Phenotype; SD, standard deviation.

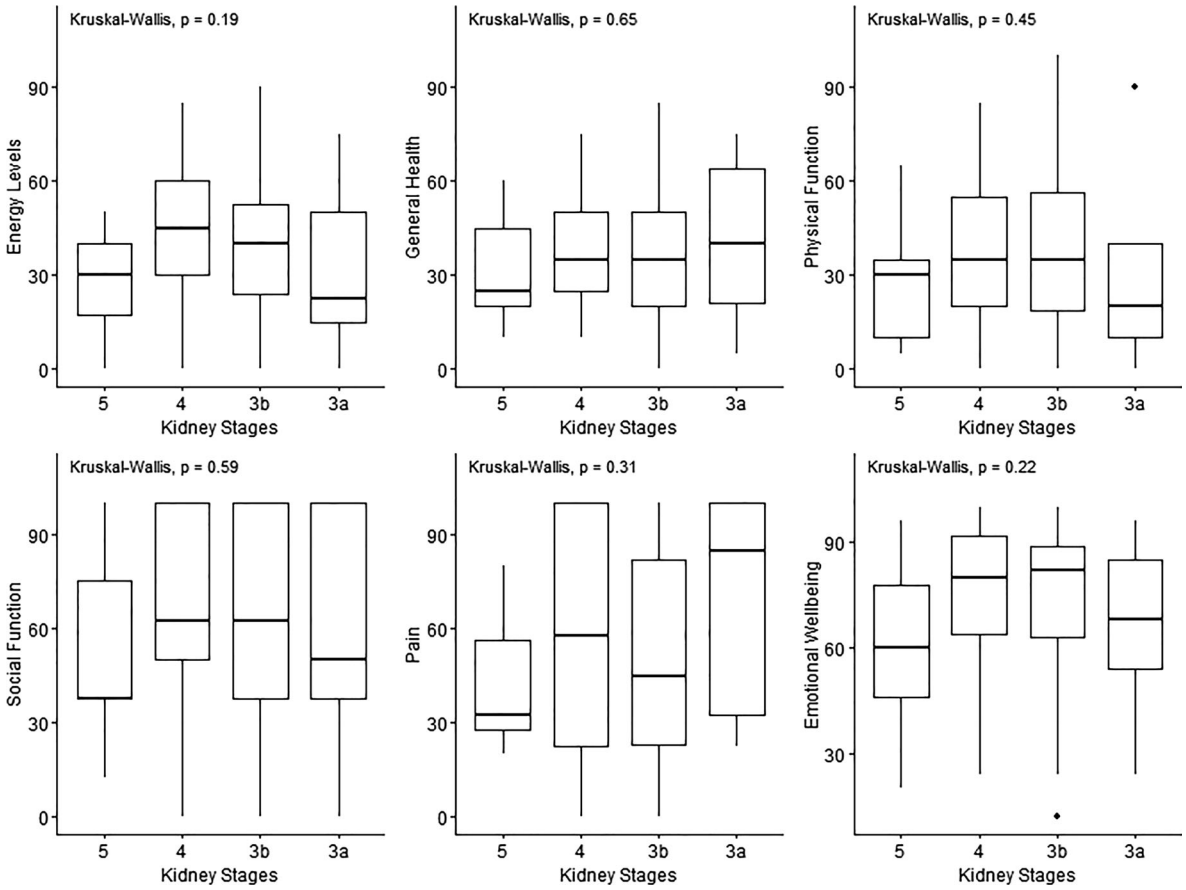
as they did not satisfy the inclusion criteria (*Figure 1*). Forty-two patients declined participation. Eight participants had unfortunately passed away by the time contact was attempted. One hundred five participants consented and were included in the study. There was no loss to follow-up; however, two participants did not complete the survey in full and were excluded.

The participants represented an older (median age 76 years), relatively diverse population (55% Caucasian, 23% Asian, 10% Black), representative of the diverse population served by the inner-city tertiary hospital in which it was conducted. The full baseline demographics are presented in *Table 2*.

Fifty-one (49.5%) participants were frail, and 52 (50.5%) were non-frail according to the MFP. Frailty according to the CFS was significantly correlated with MFP (*P*-value $<$ 0.001), providing validation of these tools. Age and BMI were not significantly associated with frailty. The median (IQR) age of participants was frail 76 (12.5) and non-frail 78.5 (12.5) (*P*-value = 0.51). The mean (SD) BMI of participants was frail 29.76 (6.66) and non-frail 27.53 (5.68) (*P*-value = 0.083). A comparison between the baseline characteristics of frail and non-frail study participants is presented in *Table 2*.

Frail patients had significantly lower HR-QOL scores in several domains. In SF-36, scores range from zero (*worst possible health state*) to 100 (*best possible health state*). Frail patients had lower physical functioning scores (frail 20.0 [IQR 10.0–32.50], non-frail 55.0 [IQR 35.0–75.0], *P*-value $<$ 0.001), general health scores (frail 30 [IQR 15.0–40.0], non-frail 40 [IQR 30–60], *P*-value $<$ 0.001), and bodily pain scores (frail 32.50 [IQR 22.50–75.0], non-frail 58.0 [IQR 37.50–100.0], *P*-value = 0.008). Frail patients also had significantly lower social functioning scores (frail 50.0 [IQR 37.50–69.0], non-frail 75.0 [IQR 62.5–100.0], *P*-value = 0.001) and energy levels (frail 25.0 [IQR 10.0–40.0], non-frail 50.0 [IQR 40.0–60.0], *P*-value $<$ 0.001). In keeping with the significantly lower physical functioning scores, frail patients had significantly worse role limitation due to physical health scores (frail 0.00 [IQR 0.0–25.0], non-frail 25.0 [IQR 0.0–75.0], *P*-value $<$ 0.001)

Figure 3 Graphs representing the relationship between chronic kidney disease stages and several parameters of HR-QOL: general health, energy, physical functioning, social functioning, bodily pain, and emotional wellbeing.



(*Figure 2*). A comparison between the baseline HR-QOL scores in frail and non-frail study participants is presented in *Table 3*.

Interestingly, there was no significant difference in emotional wellbeing (frail 76.0 [IQR 52.0–88.0], non-frail 84.0 [IQR 68.0–92.0], *P*-value = 0.121) or role limitation due to emotional health (frail 66.67 [IQR 16.50–100.0], non-frail 100.00 [IQR 66.67–100.0], *P*-value = 0.058).

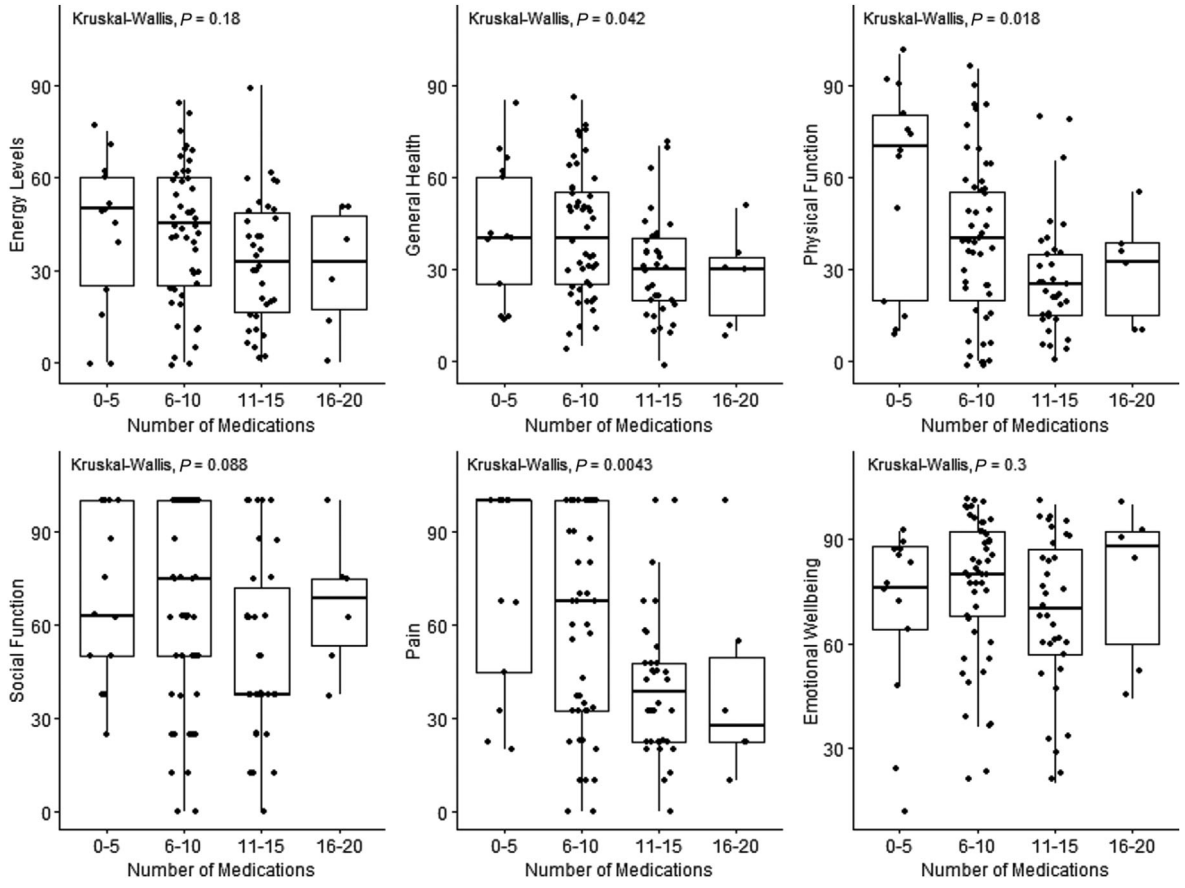
Furthermore, there was no relationship between stages 3, 4, and 5 CKD and any HR-QOL parameter: physical functioning (P = 0.705), role limitation due to physical health (P = 0.305), emotional wellbeing (P = 0.396), role limitation due to emotional problems (P = 0.401), energy (P = 0.094), social functioning (P = 0.692), pain (P = 0.707), and general health (P = 0.748) (*Figure 3*).

Similarly, EF was not correlated with frailty or quality of life scores. There was also no relationship between EF and frailty (P = 0.911). Nor was there a relationship between EF and any of the HR-QOL domains; energy (= 0.07, P = 0.48), general health (R = −0.0, P = 0.87), physical functioning (R = −1.6, P = 0.99), social functioning (R = 0.15, P = 0.14), bodily pain (R = 0.05, P = 0.59), mental health (R = −0.0, P = −0.52), role limitation due to emotional health (R = −7.0, P = 0.94), and role limitation due to physical health (R = 0.02, P = 0.85).

There was a significant relationship between polypharmacy and frailty, with frail patients taking significantly more regular medications (10.71 ± 3.00), compared with non-frail patients (8.92 ± 3.55), (P = 0.007). We divided patients into groups based on their number of regular medications (0–5, 6–10, 11–15, and 16–20). There was a statistically significant difference in median physical functioning, general health, and bodily pain scores between these groups (*P*-values = 0.018, 0.042, and 0.004, respectively) (*Figure 4*). There was no difference between groups in social functioning (P = 0.088), emotional wellbeing (P = 0.303), energy (0.176), role limitation due to emotional health (0.718), or role limitation due to physical health (0.296).

When asked to select their priority when it came to planning their healthcare, most respondents (52%) opted for 'Better Quality of Life', whilst 23% chose 'Longer Survival', and 22% selected 'Reduced Hospital Admissions' (*Figure 5*). There was no

Figure 4 Graphs representing the relationship between numbers of medications and several parameters of HR-QOL: general health, energy, physical functioning, social functioning, bodily pain, and emotional wellbeing.



significant difference between frail and non-frail patients' priorities (*P*-values = 0.495, 0.734, and 0.092 for priority one, two, and three, respectively) (*Table 2*).

Discussion

This cross-sectional study in patients with CKD-HF managed at a tertiary centre demonstrated nearly half of the cohort was frail, and that frailty was negatively associated with health-related quality of life, which patients prioritized over increased survival or avoiding hospital admissions. To our knowledge, this is the first study to evaluate this within this complex cohort of patients.

This study found high levels of frailty, consistent with other studies in CKD or HF populations.[16,24–27] Our frailty prevalence of 49.5% with a mean eGFR of 29.6 mL/min/1.73^2 was higher than other estimates in pre-dialysis CKD[15,16] and HF populations,[19] suggesting that the combination of these conditions may independently increase risk of frailty. Frailty levels observed were, however, lower than we expected when we powered the study. This study also replicated the finding from other studies that female sex is significantly associated with increased frailty.[16]

The finding of patients prioritization was recently observed in an international survey of both patients with HF and healthcare professionals who work in HF. Patients chose 'Improving overall quality of life' and 'being able to live a normal life' amongst their priority treatment objectives, in contrary to healthcare professionals who prioritized 'prolonging life' and 'reducing the number of hospitalizations'.[42] The authors recommend increased measurement and reporting of quality of life within clinical trials in order to evaluate the effect of interventions on outcomes identified as important by patients. There may also be a need to shift focus to fostering more discussions about patient priorities in clinical settings to ensure we meet patient's goal.

Frailty was significantly associated with reduced HR-QOL in several domains: physical functioning, general health, bodily pain, social functioning, energy levels, and role limitation due to physical health. This corroborates previous studies that have found a negative correlation between frailty and quality of life.[16,27] Proposed mechanisms for this relationship include that frailty is associated with weight loss, increased fatigue, weakness, mild cognitive impairment, and social exclusion, which in turn all affect an individual's functional capacity, and, consequently, quality of life.[16]

Thus, early recognition of frailty and appropriate intervention should be a priority of healthcare professionals. The stepwise cumulative deterioration of frailty should enable physicians to detect patients at risk and to deliver evidence-based interventions in order to prevent progression and to protect quality of life.[43] These interventions should encompass the following domains: physical activity, strength, balance, mobility, endurance, motor processing, nutrition, and cognition.[43–45]

Figure 5 Participants order of priority when asked to prioritize 'Longer Survival', 'Better Quality of Life' or 'Reduced Hospital Admissions'. The majority of respondents (53%) cited 'Better Quality of Life' as their first priority, when it came to planning their healthcare.

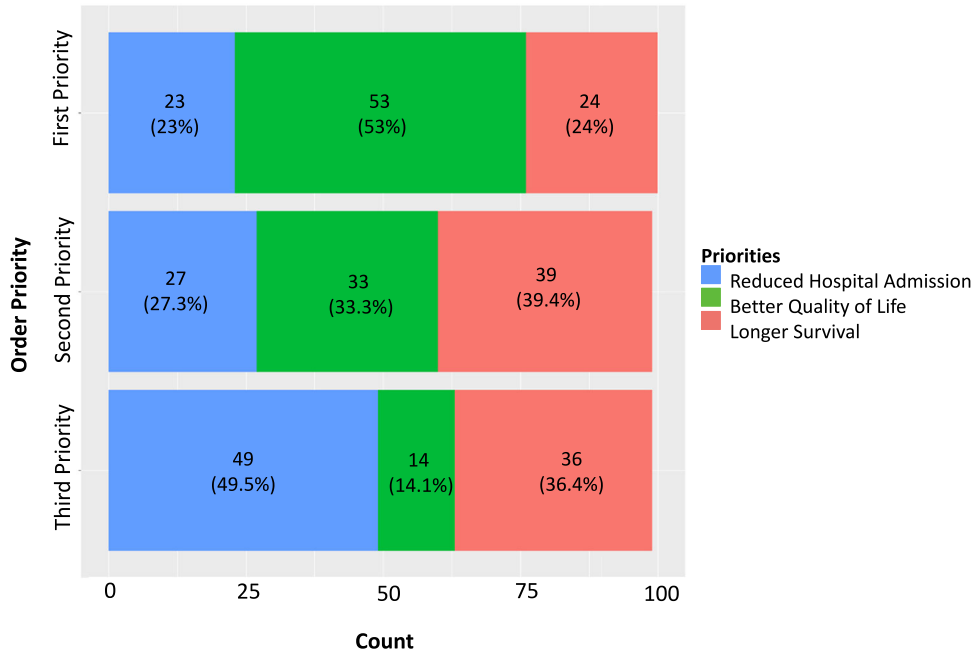


Table 4 Use of guideline-directed medical therapies and diuretics in patients in our study, by frailty status

MFP	Overall	No	Yes	
n	103	52	51	*P*-value
RAASi, No. (%)	29 (28.2)	18 (34.6)	11 (21.6)	0.210
MRA, No. (%)	67 (65.0)	33 (63.5)	34 (66.7)	0.893
Beta-blocker, No. (%)	47 (45.6)	24 (46.2)	23 (45.1)	1.000
SGLT2i, No. (%)	47 (45.6)	24 (46.2)	23 (45.1)	1.000
Diuretic, No. (%)	37 (35.9)	25 (48.1)	12 (23.5)	0.017

MFP, Modified Frailty Phenotype; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium/glucose cotransporter 2 inhibitor.

Multiple studies have been done in older adults living with frailty regarding the impact of interventions to identify and improve frailty using physical exercise and nutritional inputs.[46] Interventions have been shown to be effective for frail patients on dialysis.[47] There may be similar scope to incorporate these interventions (e.g. prescribe exercise) as part of a holistic management plan for cardiorenal patients living with frailty.

Furthermore, in this study a relationship was observed between polypharmacy and frailty, with frail patients taking significantly more regular medications than non-frail patients. We analysed whether frail patients were more or less likely to be established on the guideline-directed medical therapies for HF (i.e. renin-angiotensin aldosterone inhibitors, beta-blockers, sodium-glucose co-transporter 2 inhibitors, and mineralocorticoid receptor blockers); however, there was no statistically significant relationship observed (*Table 4*). Interestingly, in our cohort, non-frail patients were statistically significantly more likely to be taking diuretics regularly, compared with frail patients (*Table 4*). For this study, we only collected information on HF medications, so it remains unclear which classes of medication constituted the additional prescriptions taken by frail patients. It is plausible that these patients had more co-morbidities for which they were prescribed medications.

Polypharmacy has been associated with increased frailty via increased drug interactions and side-effects, increased falls, cognitive impairment, and reduced compliance with intended medication regimes.[9] However, there is also good evidence for medication optimization within frail patients, and a pre-specified post-hoc analysis from the DELIVER trial showed patients living with frailty benefited the most from treatment with dapagliflozin.[29,48]

Further incorporation of QOL/frailty outcomes in longitudinal studies will help to investigate the relationship between polypharmacy and frailty. Our study supports a person-centred approach to prescribing in this population and for physicians to consider when the addition of a new medication may, instead of resulting in the intended beneficial effect, cause a deterioration in a patient's physical and mental health.

Limitations

There are several limitations of this study. Firstly, the cross-sectional design limits inference of temporal relationships between CKD-HF, frailty and HR-QOL. Furthermore, we have evaluated a sample of patients recruited from a single centre, albeit a specialized tertiary centre interdisciplinary cardiorenal clinic. The association between worsening renal function and increasing frailty was not replicated in this study, and this may be due to the limited sample size of 103 patients with a mean eGFR of 30 mL/min/1.73^2, with $<$10% of participants with stage 5 CKD. Importantly, by employing the exclusion criterion of communication barriers and cognitive impairment, we have excluded some of the frailest patients in this population. Furthermore, several patients who declined participation cited poor health as their reason for doing so, meaning that the respondents to this survey are likely healthier than the overall cohort of patients with CKD-HF.

Conclusions

To our knowledge, this is the first study that has evaluated the relationship between frailty and HR-QOL within CKD-HF.

Frailty is significantly associated with reduced HR-QOL in several domains in patients with CKD-HF. HR-QOL is a priority for patients. Frailty should be considered as an important and modifiable factor in maintaining HR-QOL, and thus, healthcare professionals should recognize the importance of early detection and intervention of frailty. Longitudinal studies are needed to evaluate interventions to reduce frailty and consequently improve quality of life in patients with CKD-HF.

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Conflict of interest

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

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