Associations between frailty trajectories and cardiovascular, renal, and mortality outcomes in chronic kidney disease

Thomas J. Wilkinson¹,²*, Joanne Miksza³, Francesco Zaccardi⁴, Claire Lawson³, Andrew C. Nixon⁵, Hannah M.L. Young⁶,⁷, Kamlesh Khunti¹,⁴ & Alice C. Smith²,⁸

¹NIHR Applied Research Collaboration East Midlands, Leicester Diabetes Research Centre, Leicester, UK; ²Leicester Kidney Lifestyle Team, Department of Health Sciences, University of Leicester, Leicester, UK; ³Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; ⁴Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK; ⁵Lancashire Teaching Hospitals NHS Foundation Trust, Lancashire, UK; ⁶Leicester Diabetes Centre, University Hospitals of Leicester NHS Trust, Leicester, UK; ⁷Department of Respiratory Sciences, University of Leicester, Leicester, UK; ⁸Leicester NIHR Biomedical Research Centre, Leicester, UK

Abstract

Background  Frailty is characterized by the loss of biological reserves and vulnerability to adverse outcomes. Individuals with chronic kidney disease (CKD), numerous pathophysiological factors may be responsible for frailty development including inflammation, physical inactivity, reduced energy intake, and metabolic acidosis. Given that both CKD and frailty incur a significant healthcare burden, it is important to understand the relationship of CKD and frailty in real-world routine clinical practice, and how simple frailty assessment methods (e.g. frailty indexes) may be useful. We investigated the risk of frailty development in CKD and the impact of frailty status on mortality and end-stage kidney disease (ESKD).

Methods  A retrospective cohort study using primary care records from the Clinical Practice Research Datalink linked to Hospital Episode Statistics and the UK Office for National Statistics was undertaken in 819,893 participants aged ≥40 years, of which 140,674 had CKD. Frailty was defined using an electronic frailty index, generated electronically from primary care records. Cox proportional hazard and flexible parametric survival models were used to investigate the risk of developing frailty and the effect of frailty on risk of all-cause and cardiovascular-related mortality, and ESKD.

Results  The mean age of those with CKD was 77.5 (SD 9.7) years [61.0 (SD 12.1) years in no-CKD group]; 62.0% of the CKD group were female (compared with 53.3% in no-CKD group). The mean estimated glomerular filtration rate of those with CKD was 46.1 (SD 9.9) mL/min/1.73 m². The majority of those with CKD (75.3%) were frail [vs. 45.4% in those without CKD (no-CKD)]. Over 3 years (median), 69.5% of those with CKD developed frailty. Compared with no-CKD, those with CKD had increased rates of developing mild (hazard ratio: 1.02; 95% confidence interval: 1.01–1.04), moderate (1.30; 1.26–1.34), and severe (1.50; 1.37–1.65) frailty. Mild (1.22; 1.19–1.24), moderate (1.60; 1.56–1.63), and severe (2.16; 2.11–2.22) frailty was associated with increased rates of all-cause and cardiovascular-related mortality (mild 1.35; 1.31–1.39; moderate 1.96; 1.90–2.02; and severe 2.91; 2.81–3.02). All stages of frailty significantly increased ESKD rates.

Conclusions  Frailty is highly prevalent and associated with adverse outcomes in people with CKD, including mortality and risk of ESKD. Preventative interventions should be initiated to mitigate the development of frailty. The use of a simple frailty index, generated electronically from health records, can predict outcomes and may aid prioritization for management of people with frailty.

Keywords  Chronic kidney disease; Frailty; Mortality; Dialysis; Epidemiology

Received: 1 February 2022; Revised: 11 April 2022; Accepted: 25 June 2022
*Correspondence to: Thomas J. Wilkinson, NIHR Applied Research Collaboration East Midlands, Leicester Diabetes Research Centre, Leicester, UK. Email: t.j.wilkinson@leicester.ac.uk

© 2022 The Authors. Journal of Cachexia, Sarcopenia and Muscle published by John Wiley & Sons Ltd on behalf of Society on Sarcopenia, Cachexia and Wasting Disorders. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
Introduction

Frailty is defined as a biological syndrome characterized by decreased physiological reserves, which puts an individual at increased vulnerability to adverse outcomes when facing minor stressors.\(^1\) Frailty has been described as the physical state that exists before occurrence of disability; however, it is possible for both to coexist. Frailty is a dynamic in that it can exist on a continuum from fit to frail and may change in either direction over time. Frailty is therefore potentially reversible, and its associated functional decline is also a potentially preventable disability.\(^3\) The estimated frailty prevalence is ~15% for adults aged ≥65 years and >25% in those aged >85 years.\(^4\)

Screening for frailty is recommended internationally with recently developed evidence-based clinical practice guidelines for frailty management.\(^3,5\) Routine frailty identification is national policy in the UK\(^6\) with recommendations that healthcare providers in primary care should proactively identify cases of moderate and severe frailty.\(^7\) The worldwide prevalence of chronic kidney disease (CKD) is ~9%, with most patients managed in primary care settings.\(^8\) The prevalence of frailty is high in CKD, although estimates differ in the population and operational definition used.\(^9\) Various contributing pathophysiological factors are responsible for frailty in CKD including inflammation, inactivity, reduced energy intake, and metabolic acidosis.\(^9-12\) Whether CKD contributes to the incidence of frailty over time is unclear.\(^13\)

With no definite means of assessment, a phenotype model of physical frailty is often used.\(^9,11,14\) However, its assessment is somewhat limited in clinical practice because of its lack of standardization and need for objective function measures. Alternatively, a contrasting and more holistic approach is the use of a frailty index, based on the cumulative deficit model of frailty.\(^10\) Irrespective of the method used, frailty is independently linked with adverse outcomes across all CKD stages, including an increased symptom burden, risk of mortality, hospitalization, and falls, as well as reduced quality of life, physical, and cognitive functioning.\(^9,11,12,14-20\)

With recommendations that healthcare providers should be actively attempting to identify frail CKD patients,\(^3,10,14\) simple and early identification of frailty could result in improvements in those referred to and treated in secondary care and specialist services. Given that both CKD and frailty incur a significant healthcare burden, it is important to understand the relationship of CKD and frailty in real-world routine clinical practice, and how simple frailty assessment methods (e.g. frailty indexes) may be useful. Using a large contemporary data set from UK primary care, the aims of this study were as follows: (i) to describe the prevalence of frailty in those with and without CKD (no-CKD); (ii) to investigate changes in frailty status (i.e. trajectories of frailty) in non-frail individuals; (iii) to explore the relationship between frailty and all-cause and cardiovascular mortality, stratified by frailty level; and (iv) to explore the association between frailty level and rates of incident dialysis and kidney transplantation.

Materials and methods

Data sources

A retrospective observational cohort study utilizing the Clinical Practice Research Datalink (CPRD) was undertaken. The CPRD is an ongoing UK primary care database of anonymized longitudinal medical records, with coverage of ~19 million people from >700 healthcare practices. With >7 million active patients meeting eligibility (i.e. alive and currently registered at contributing practices), ~13% of the population are included.\(^21,22\) Patients included in the database are broadly representative of the general population in terms of age, sex, ethnicity, and validated diagnoses.\(^22\) To gain a comprehensive information on ethnicity and outcomes, we used ~60% of CPRD data that were linked to Hospital Episode Statistics (HES). The data were also linked to the Index of Multiple Deprivation, a validated method of socio-economic status. This study was approved by the independent scientific advisory committee for CPRD research (protocol reference: 19/157).

Study population

We used data for a random selection of 1 million patients (the maximum allowed by CPRD), recorded aged ≥40 years, and who were registered on CPRD between 1 January 2006 and 31 December 2015 with linkage to HES and Office for National Statistics, for mortality data. Patients must have been registered in the practice for ≥12 months and have at ≥2 consecutive serum creatinine levels. We excluded patients on prevalent kidney replacement therapy (haemodialysis, peritoneal dialysis, or kidney transplantation).

CKD cohort

Patients with biochemical evidence of CKD Stages 3a–5 were identified by two consecutive measurements of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m\(^2\) separated by >90 days.\(^23\) eGFR was calculated from serum creatinine records using the Chronic Kidney Disease Epidemiology Collaboration equation.\(^24\) Patients were included in the CKD cohort on the date when their second eGFR was <60 mL/min/1.73 m\(^2\) (index date). Patients were stratified into CKD stages: 45–60 mL/min/1.73 m\(^2\) (3a); 30–44 mL/min/1.73 m\(^2\) (3b); 15–29 mL/min/1.73 m\(^2\) (4), and <15 mL/min/1.73 m\(^2\) (5).
Comparison cohort (no-CKD)

To define a comparison group, people without known CKD were selected from the remaining study population.

Frailty

Frailty status was identified using an electronic frailty index (eFI).²⁵ The eFI uses a cumulative deficit model of frailty to calculate an index based on the presence or absence of 36 individual deficits, which are constructed using 2171 electronic healthcare record codes. These include mobility and cognitive problems, arthritis, osteoporosis, diabetes, dyspnoea, falls, weight loss and anorexia, and ischaemic heart disease. A full list of deficits can be found in Supporting Information, Table S1. The eFI is supported by the UK National Institute for Health and Care Excellence multimorbidity guidelines²⁶ and can be electronically generated easily.²⁷ For this analysis, to investigate the role of the index independent of CKD, we used a modified eFI as we removed CKD, one of the deficits originally included. Previously defined frailty categories were used: non-frail (≤4 deficits); mild frailty (5–8 deficits); moderate frailty (9–12 deficits); and severe frailty (≥13 deficits).²⁵

Statistical analysis

Summary measures were described using mean [standard deviation (SD)] or median [inter-quartile range (IQR)] for continuous variables and as a count (%) for categorical variables. Means were compared using a two-sample t-test, medians with a two-sample Wilcoxon test, and count data using a χ² test. Analysis was conducted using Stata 17.0 (StataCorp) and R 4.1.1; P-values <0.05 were considered statistically significant.

Aims 1 and 2

For the initial analysis, participants with ≥5 frailty deficits at index date were excluded. Cox proportional hazard survival models with CKD exposure as a time-varying covariate were fitted with time from index date until event/censoring as the timescale. An event was defined as the occurrence of frailty (≥5 deficits), and censoring took place on the first incidence of death, transfer out of practice, or last data collection date for practice. Both unadjusted and adjusted models were fitted, with sex, social deprivation, age, and ethnicity identified a priori as confounders. Models were stratified by CKD status, and analyses were performed with thresholds for frailty event corresponding to mild, moderate, and severe frailty. A non-stratified adjusted model was fitted with CKD status included as a covariate to check the significance of CKD exposure on development of frailty. Incidence rates were calculated per 100 person years.

Aim 1: prevalence of frailty in the CKD and non-CKD cohorts

Frailty prevalence, stratified by CKD stage, is shown in Figure 2. The majority of individuals with CKD were frail (75.3% had mild frailty or worse, compared with 45.4% in those without CKD, P < 0.001). The highest prevalence of moderate and severe frailty was found in the advanced CKD stages (4 and 5), and in Stage 4, 87.2% were frail. The median (IQR) number of deficits in the CKD group was 7 (IQR 5–9)/35, compared with 4 (IQR 3–6)/35 in the no-CKD group. The three greatest
deficits contributing to the eFl in the CKD group were as follows: (i) polypharmacy (83.7%); (ii) hypertension (65.8%); and (iii) anaemia and hematinic deficiency (56.9%) (Table S1).

**Aim 2: development of frailty in non-frail CKD and no-CKD cohorts**

After exclusion of baseline pre-existing frailty (Figure 1), a total of 405,719 ‘non-frail’ participants were included in this analysis, of which 34,791 (8.6%) had CKD. In those with CKD, the mean age was 73.0 (SD 10.1) years, 42.5% were male, and 97.0% were White. Mean eGFR was 48.8 (SD 8.8) mL/min/1.73 m². Almost half (48.8%) of the CKD group had hypertension and 12.6% had diabetes (full characteristics for these participants are shown in Table S4).

### Risk of developing frailty

During a median follow-up time of 3.0 (IQR 1.3–5.4) years, of the 34,791 participants with CKD, 69.5% (n = 24,187) developed frailty: 54.1% (n = 18,856) developed mild, 13.6% (n = 4,731) moderate, and 1.7% (n = 600) severe frailty. In those without CKD, 160,142 out of 370,928 (43.2%) developed frailty (mild 38%, moderate 4.6%, and severe 0.5%). The incidence rate for developing mild frailty was 15.81 per 100 person years in the CKD group and 10.32 in the no-CKD group (incidence rate ratio 1.53 [95% confidence interval (CI): 1.52–1.54]) (Figure 3).

In non-frail participants at baseline, those with CKD had a small, yet significant, 2% increased rate of developing mild frailty [hazard ratio (HR): 1.02; 95% CI: 1.01–1.04; P < 0.001], a 30% increased rate of developing moderate frailty (1.30; 1.26–1.34; P < 0.001), and a 50% increased rate of severe frailty (1.50; 1.37–1.65; P < 0.001), compared with the no-CKD group. The development of frailty did not differ between CKD stages.

### Aim 3: relationship between frailty with all-cause and cardiovascular mortality in a CKD and no-CKD population stratified by frailty level

In total, 213,316 died during the follow-up period (median, 5.3 years). The incidence rate in the CKD group was between 9.50 (mild frailty) and 21.43 (severe frailty) per 100 person years in the CKD group and 10.32 in the no-CKD group (incidence rate ratio 1.53 [95% confidence interval (CI): 1.52–1.54]) (Figure 3).

In non-frail participants at baseline, those with CKD had a small, yet significant, 2% increased rate of developing mild frailty [hazard ratio (HR): 1.02; 95% CI: 1.01–1.04; P < 0.001], a 30% increased rate of developing moderate frailty (1.30; 1.26–1.34; P < 0.001), and a 50% increased rate of severe frailty (1.50; 1.37–1.65; P < 0.001), compared with the no-CKD group. The development of frailty did not differ between CKD stages.

In total, 213,316 died during the follow-up period (median, 5.3 years). The incidence rate in the CKD group was between 9.50 (mild frailty) and 21.43 (severe frailty) per 100 person years, compared with 4.05 (mild frailty) and 15.01 (severe frailty) in the no-CKD group (Table S5). Table 2 shows HRs for all-cause and cardiovascular-related mortality in the CKD and no-CKD groups. In those with CKD, compared with being ‘non-frail’, mild frailty increased the rates of all-cause mortality by 22% (HR: 1.22; 95% CI: 1.19–1.24; P < 0.001), severe frailty by 52% (HR: 1.52; 95% CI: 1.47–1.57; P < 0.001), and cardiovascular mortality by 32% (HR: 1.32; 95% CI: 1.27–1.37; P < 0.001).
moderate frailty by 60% (1.60; 1.56–1.63; P < 0.001), and severe frailty by 116% (2.16; 2.11–2.22; P < 0.001).

In the no-CKD group, frailty increased the rates of all-cause mortality by 28–139% (Figure S1 shows Kaplan–Meier plots). Figure 4 shows predicted survival up to 10 years by frailty level at baseline in both CKD and no-CKD groups: there were small (<1%) yet significant differences between 10 year predicted survival between CKD and no-CKD within each frailty level (Table S7).

Frailty was associated with increased cardiovascular mortality in those with and without CKD. Subjects with CKD

Table 1 Overall participant demographics and characteristics

|                     | CKD       | No-CKD    | P-value |
|---------------------|-----------|-----------|---------|
| N                   | 140 674   | 679 219   | <0.001  |
| Age (years)         | 77.5 (SD 9.7) | 61.0 (SD 12.1) | <0.001  |
| Sex, female n (%)   | 87 188 (62.0%) | 362 285 (53.3%) | <0.001  |
| Ethnicity           |           |           | <0.001  |
| White, n (%)        | 137 057 (97.4%) | 634 708 (93.4%) | <0.001  |
| Black, n (%)        | 710 (0.5%) | 12 143 (1.8%) |           |
| Asian, n (%)        | 1681 (1.2%) | 19 404 (2.9%) |           |
| Mixed/other, n (%)  | 1226 (0.9%) | 12 964 (1.9%) |           |
| eGFR (mL/min/1.73 m²) | 46.1 (SD 9.9) | 81.3 (SD 15.1) | <0.001  |
| Stage 3a, n (%)     | 86 171 (61.3%) | — |           |
| Stage 3b, n (%)     | 43 520 (30.9%) | — |           |
| Stage 4, n (%)      | 10 405 (7.4%) | — |           |
| Stage 5, n (%)      | 578 (0.4%) | — |           |
| Social deprivation status |         |           | <0.001  |
| Q1 (least deprived), n (%) | 8767 (25.2%) | 94 305 (25.4%) | <0.001  |
| Q2, n (%)           | 8499 (24.4%) | 85 314 (23.0%) |           |
| Q3, n (%)           | 7467 (21.5%) | 77 324 (20.9%) |           |
| Q4, n (%)           | 5919 (17.0%) | 65 578 (17.7%) |           |
| Q5 (most deprived), n (%) | 4122 (11.9%) | 48 186 (13.0%) | <0.001  |
| eFI deficits (n)    | 7 (IQR 5–9) | 4 (IQR 3–6) | <0.001  |
| Comorbidities a     |           |           | <0.001  |
| Diabetes, n (%)     | 31 678 (22.5%) | 107 131 (15.8%) | <0.001  |
| Falls, n (%)        | 47 228 (33.6%) | 110 084 (16.2%) |           |
| Hypertension, n (%) | 92 553 (65.8%) | 276 808 (40.8%) |           |
| Ischaemic heart disease, n (%) | 62 804 (44.6%) | 234 627 (34.5%) |       |
| Polypharmacy b, n (%) | 525 769 (77.4%) | 117 798 (83.7%) |           |
| Respiratory disease, n (%) | 47 676 (33.9%) | 200 107 (29.5%) |           |

CKD, chronic kidney disease; eFI, electronic frailty index; eGFR, estimated glomerular filtration rate; IQR, inter-quartile range; SD, standard deviation.

Unless otherwise stated, data shown as mean (SD), median (IQR), or number (%).

aComorbidities taken from deficits used to calculate eFI; full deficits can be found in the Supporting Information.

bPolypharmacy is defined based on the presence of ≥5 prescribed medications, using Chapters 1–15 of the British National Formulary.

Figure 2 Prevalence of frailty in the chronic kidney disease (CKD) and no-CKD cohorts. Frailty defined using eFI: non-frail (≤4 deficits present); mild frailty (5–8 deficits present); moderate frailty (9–12 deficits present); and severe frailty (≥13 deficits present). Data used to generate figure found in Table S3.

Figure 3 Incidence rate of developing frailty for chronic kidney disease (CKD) and no-CKD groups. Data used to generate figure found in Table S5. CI, confidence interval.

Figure 4 shows predicted survival up to 10 years by frailty level at baseline in both CKD and no-CKD groups: there were small (<1%) yet significant differences between 10 year predicted survival between CKD and no-CKD within each frailty level (Table S7).

Frailty was associated with increased cardiovascular mortality in those with and without CKD. Subjects with CKD
and moderate (HR: 1.96; 1.90–2.02; \(P < 0.001\)) and severe frailty (2.91; 2.81–3.02; \(P < 0.001\)) had a two-fold to three-fold increased risk, compared with those non-frail.

**Aim 4: association between frailty level and rates of incident dialysis and kidney transplantation in subjects with CKD**

In total, 724 (\(<1\%\)) subjects initiated dialysis during the follow-up period (median, 4.8 years). Compared with non-frail, the incidence rate ratios were 1.20 for mild frailty, 1.04 for moderate frailty, and 11.0 for severe frailty (Table S8). In those with CKD, compared with being ‘non-frail’, mild (HR 1.50; 1.16–1.94; \(P < 0.001\)), moderate (1.63; 1.24–2.31; \(P < 0.001\)), and severe (2.02; 1.28–3.19; \(P < 0.001\)) frailty all increased the rates of requiring dialysis (Table 3). An insufficient number of patients (\(n = 62\)) received a transplant to warrant analysis.

**Discussion**

In view of the population living longer, frailty is an important health policy issue, and there is growing acknowledgement that healthcare systems need to adapt to meet the needs of people living with frailty. In the UK, each year, frailty costs £5.8bn, with severe frailty costing an additional £2100 per patient through additional consultations and admissions. Using a large data set of UK primary care records, we found that three in four people with CKD have frailty, with worse frailty in those with advanced CKD. We observed an association between CKD and frailty, with CKD increasing the risk of developing frailty over
time. Frailty was associated with greater all-cause and cardiovascular-related mortality, and an increased risk of requiring dialysis.

**Frailty prevalence**

Frailty is difficult to diagnose, and estimating frailty prevalence in CKD is challenging because of the different and competing criteria used. In a systematic review by Chowdhury et al.,9 frailty prevalence ranged from 7% in community dwellers (Stages 1–4) to 73% in hemodialysis patients. The majority of studies conducted in CKD use variations of the Fried phenotype, a measure of (physical) frailty, which uses objective measures of physical performance, activity, and weight loss, as well as an indicator of fatigue/exhaustion. However, it is often modified to accommodate different criteria and appears limited in grading severity when frailty prevalence is high.1

In our cohort, using an eFI, most (75.3%) CKD patients had mild frailty or worse, and in those with advanced disease, ~8 in 10 patients were frail. Current policy in the UK recommends identification of all patients aged ≥65 with moderate or severe frailty; in our data, >30% of CKD patients fulfilled these criteria. Whilst no other studies have reported the use of the eFI in non-dialysis CKD, our numbers are higher than seen in individuals without CKD, where 7.7% had moderate frailty and 1.3% had severe frailty. Clegg et al.25 previously found that the eFI classified 12% of adults >65 years as moderately frail and 3% as severely frail. A possible explanation for the high prevalence of frailty seen in our cohort is the mean age of our CKD group was 77.5 years, and as such, our data align more suitably to that of Lansbury et al.,27 who showed 36.0% patients aged ≥75 had mild, 32.0% as moderate, and 11.7% as severe frailty. The eFI may also overestimate frailty in older people.30

**Development of frailty**

Whether CKD itself contributes to frailty over time remains unclear.13 Our findings showed that, over an ~3 year period, CKD independently increased the risk of developing frailty compared with those without CKD. In our data, over half of CKD patients developed frailty; the incidence rate of developing mild frailty in those with CKD was 15.81 per 100 person years (i.e. 16 people out of 100 CKD patients will develop mild frailty each year, compared with 10 in the no-CKD group). Previously, Guerville et al.31 found that frailty, using the Fried phenotype, occurred in 14% of 1201 participants from the ‘Multidomain Alzheimer Preventive Trial’ during a 5 year follow-up period. Here, whilst baseline eGFR was not associated with frailty incidence, faster eGFR decline (~4.1 mL/min/1.73 m² per year) was. Dalrymple et al.32 found that among non-frail participants, lower eGFR was associated with a higher risk of incident frailty. In particular, those with an eGFR between <45 mL/min/1.73 m² were twice as likely to develop frailty over 4 years compared with those with normal eGFR.

**Frailty and adverse outcomes**

In individuals with CKD, compared with being ‘non-frail’, frailty increased the risk of all-cause mortality. We found a higher mortality risk with increasing frailty severity, independent of age, sex, social deprivation, and ethnicity. Our findings suggest that in those with moderate and severe frailty, the rates of all-cause mortality are increased by ~60% to 116%. This supports a plethora of data from meta-analyses and systematic reviews.9,11,17 For example, Mei et al.26 found that pre-frailty and frailty were related to mortality, with a pooled HR of 1.68 and 1.48, respectively, and in Zhang et al.,11 12 studies involving 127 373 participants suggested that frailty increased the mortality risk in patients with CKD, especially in dialysis patients. The majority of studies investigating frailty in CKD have taken place almost exclusively in the USA.9,11 To our knowledge, only one study33 has investigated frailty and mortality risk in a UK non-dialysis CKD population. Whilst this study was limited by a relatively small sample size, frailty (assessed by the Clinical Frailty Scale during a home visit) was an independent predictor of mortality in patients referred for ‘pre-dialysis education’. None of the studies aforementioned used the eFI as in our current study. Only one other report has used the eFI in a CKD population: preliminary results from the ‘Connected

---

**Table 3** Frailty and risk of dialysis in those with CKD

|                  | Unadjusted | P-value | Adjusted* | P-value |
|------------------|------------|---------|-----------|---------|
| Non-frail        | 1.00 (ref) | —       | 1.00 (ref)| —       |
| Mild frailty     | 1.19 (0.96–1.47) | 0.116     | 1.50 (1.16–1.94) | <0.001 |
| Moderate frailty | 1.07 (0.83–1.38) | 0.619     | 1.63 (1.24–2.31) | <0.001 |
| Severe frailty   | 1.27 (0.84–1.91) | 0.256     | 2.02 (1.28–3.19) | <0.001 |

CKD, chronic kidney disease.
Data shown as hazard ratios and upper/lower 95% confidence intervals.

*Adjusted model for age, sex, social deprivation, CKD stage, and ethnicity.
Frailty trajectories and outcomes in CKD

Health Cities—Connected Bradford’ initiative, which linked data sets from 492 patients undergoing dialysis, showed that the eFI was associated with mortality. The median deficit score of this cohort was 7, the same as our cohort, and the authors concluded that the eFI is likely to have prognostic utility in ESKD patients. In our data, there were small (<1%) differences between 10 year predicted survival between CKD and no-CKD within each frailty level, suggesting that whilst CKD does marginally affect survival, frailty has a larger effect overall.

We found that frailty increased the rates of progression to dialysis by two-fold when compared with those non-frail. Frailty has previously been investigated in people on dialysis (e.g. Fitzpatrick et al.), although few studies have explored whether frailty increases the risk of dialysis. Using the frailty phenotype, Bao et al. found that patients starting dialysis at a higher eGFR were more likely to be frail. There are several reasons why frail patients might be initiated on dialysis earlier, including underestimation of kidney function, uraemia, malnutrition, and comorbidity. Frailty has also been associated with faster eGFR decline, which may result in earlier initiation.

The mechanisms that contribute to frailty in CKD are multifaceted and include protein-energy wasting, uraemic toxin accumulation, cognitive impairment, inflammation, inactivity, and anaemia. The deficits contributing to the eFI were more prevalent among individuals with CKD, and given that many of these deficits include common symptoms and comorbidities of CKD (e.g. sleep disturbance and diabetes), it may be the eFI performs as a surrogate indicator of symptom and comorbidity severity. Nevertheless, with no established assessment of frailty and an emphasis placed on any effort to identify frailty in CKD, the eFI appears a suitable risk stratification tool that balances practicality and predictive power.

**Frailty management**

As frailty may be modifiable, recommendations both internationally and in the UK suggest that for patients identified as frail, an annual medicines review and falls risk assessment should be performed. Given its complex nature, the management of frailty in CKD is multifaceted and multidisciplinary. Such management is likely to involve formal diagnostic and treatment processes (e.g. the Comprehensive Geriatric Assessment) and subsequent person-centred management strategies [e.g. medication review, nutrition, care of complications (e.g. fluid overload and acidosis), management of mental health, rehabilitation, and, where appropriate, advance care planning].

Our evidence suggests that CKD may predispose patients to frailty; therefore, early preventative multidimensional interventions to mitigate this course should be considered. Following national guidance in the UK, those with moderate and severe frailty most at risk of adverse outcomes should be actively identified to ensure prompt and effective management.

**Strengths, limitations, and future work**

A key strength of our study is the use of CPRD. The use of the CPRD in CKD is growing having been used to investigate associations between CKD and dementia. CPRD is characterized by its large coverage, longitudinal follow-up, representativeness, linkages, and data quality processes. Previous study has shown that the CPRD captures most people with decreased kidney function (eGFR < 60 mL/min/1.73 m²), compared with nationally representative statistics, based on blood test results. We used two eGFR values to define CKD as per international criteria, although acknowledging this may fail to accurately capture people with transient changes in eGFR (e.g. as a result of acute kidney injury). We were able to adjust for different confounders likely to influence both CKD and frailty; however, residual confounders may still exist. We were unable to account for the severity of worsening comorbidity over time, which may partly explain the findings (e.g. progression of heart failure or respiratory disease). In those with CKD, we decided to remove CKD as deficit in the calculation of the eFI, and this may have resulted in an underestimation of frailty in our cohort. Further work could explore the confounding effects of other CKD-related biomarkers such as albumin. In addition, investigating the association of frailty regression (i.e. improvement in deficits) on outcomes may help facilitate targets for future interventions.

**Conclusions**

In summary, in people living with CKD, frailty is highly prevalent and predictive of adverse outcomes, including all-cause and cardiovascular mortality, and dialysis. We found that CKD independently increased the risk of developing frailty. Our study highlights the importance of routinely assessing frailty, particularly moderate and severe, among patients with CKD with a view to considering targeted interventions that aim to improve prognosis. The use of a simple frailty index, like the eFI, in routine primary care could represent a major advance in the care of CKD patients with frailty, and preventative multidimensional interventions should be instigated early to mitigate the development of frailty in this group.
Acknowledgements

We would like to thank Professor Andrew Clegg for his advice and resources regarding the use and generation of the eFI. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle.41

Conflict of interest

None declared.

Funding

This work was supported by the Stoneygate Trust, NIHR Applied Research Collaboration East Midlands (ARC-EM), NIHR Leicester Biomedical Research Centre, and Leicester Real World Evidence Unit, University of Leicester. The independent scientific advisory committee (ISAC) for CPRD research approved this study (protocol reference: 19/157). H.M.L.Y. is supported by an NIHR Development and Skills Enhancement Award. The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752–762.
2. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.
3. Dent E, Martin FC, Bergman H, Woo J, Romero-Ortuno R, Walston JD. Management of frailty: opportunities, challenges, and future directions. Lancet 2019;394:1376–1386.
4. Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodriguez-Manas L, Fried LP, et al. Physical frailty: ICFSR international clinical practice guidelines for identification and management. J Nutr Health Aging 2019;23:771–787.
5. Dent E, Lien C, Lim WS, Wong CH, Ng TP, et al. The Asia-Pacific clinical practice guidelines for the management of frailty. J Am Med Dir Assoc 2017;18:545–576.
6. NHS England. GP Contract documentation 2017/18. Available at: https://www.england.nhs.uk/gp/investment/gp-contract/gp-contract-documentation-2017-18/ Accessed: 10/11/2021.
7. NHS. Long Term Plan. 2019. Available at: https://www.longtermplan.nhs.uk/ Accessed: 10/11/2021.
8. Kim LG, Caplin B, Cleary F, Hull SA, Griffith K, Wheeler DC, et al. Accounting for overdosing when determining primary care outliers for the identification of chronic kidney disease: learning from the National Chronic Kidney Disease Audit. Nephrol Dial Transplant 2017;32:151–158.
9. Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and chronic kidney disease: a systematic review. Arch Gerontol Geriatr 2017;68:135–142.
10. Nixon AC, Bampouras TM, Pendleton N, Woywodt A, Mitra S, Dhaygude A. Frailty and chronic kidney disease: current evidence and continuing uncertainties. Clin Kidney J 2018;11:236–245.
11. Zhang Q, Ma Y, Lin F, Zhao J, Xiong J. Frailty and mortality among patients with chronic kidney disease and end-stage renal disease: a systematic review and meta-analysis. Int Urol Nephrol 2020;52:363–370.
12. Walker SR, Wagner M, Tangri N. Chronic kidney disease, frailty, and unsuccessful aging: a review. J Ren Nutr 2014;24:364–370.
13. Delgado C. Frailty and CKD: chicken or the egg? Clin J Am Soc Nephrol 2019;14:1554–1556.
14. Worthen G, Tennankore K. Frailty screening in chronic kidney disease: current perspectives. Int J Nephrol Renovasc Dis 2019;12:229–239.
15. Nixon A, Wilkinson T, Young H, Taal MW, Pendleton N, Mitra S, et al. Symptom burden in people living with frailty and chronic kidney disease. BMC Nephrol 2020;21:1–11.
16. Nixon AC, Bampouras TM, Pendleton N, Mitra S, Brady ME, Dhaygude AP. Frailty is independently associated with worse health-related quality of life in chronic kidney disease: a secondary analysis of the Frailty Assesment in Chronic Kidney Disease study. Clin Kidney J 2020;13:85–94.
17. Mei F, Gao Q, Chen F, Zhao L, Shang Y, Hu K, et al. Frailty as a predictor of negative health outcomes in chronic kidney disease: a systematic review and meta-analysis. J Am Med Dir Assoc 2021;22:535–543.e537.
18. McAdams-DeMarco MA, Tan J, Salter ML, Gross A, Meoni LA, Jaar BG, et al. Frailty and cognitive function in incident hemodialysis patients. Clin J Am Soc Nephrol 2015;10:2181–2189.
19. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N, et al. Frailty and mortality in kidney transplant recipients. Am J Transplant 2015;15:149–154.
20. Delgado C, Grimes BA, Glidden DV, Shlipak M, Sarnak MJ, Johansen KL. Association of frailty based on self-reported physical function with directly measured kidney function and mortality. BMC Nephrol 2015;16:203.
21. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol 2019;48:1740–1740.
22. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–836.
23. National Institute for Health and Care Excellence (NICE). Chronic kidney disease: assessment and management NICE guideline [NG203]. Available at: https://www.nice.org.uk/guidance/ng203 Accessed: 10/11/2021.
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HJ, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
25. Clegg A, Bates C, Young J, Ryan R, Nichols L, Teale EA, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing 2016;45:353–360.
26. National Institute for Health and Care Excellence (NICE). Multimorbidity: clinical assessment and management. NICE guideline [NG56] Available at: https://www.nice.org.uk/guidance/ng56 Accessed: 10/11/2021.

27. Lansbury LN, Roberts HC, Clift E, Herklots A, Robinson N, Sayer AA. Use of the electronic Frailty Index to identify vulnerable patients: a pilot study in primary care. *Br J Gen Pract* 2017;*67*:751–756.

28. Reeves D, Pye S, Ashcroft DM, Clegg A, Kontopantelis E, Blakeman T, et al. The challenge of ageing populations and patient frailty: can primary care adapt? *BMJ* 2018;362:k3349.

29. Han L, Clegg A, Doran T, Fraser L. The impact of frailty on healthcare resource use: a longitudinal analysis using the Clinical Practice Research Datalink in England. *Age Ageing* 2019;48:665–671.

30. Broad A, Carter B, Mckelvie S, Hewitt J. The convergent validity of the electronic frailty index (eFI) with the Clinical Frailty Scale (CFS). *Geriatrics (Basel)* 2020;5.

31. Guerville F, de Souto BP, Taton B, Bourdel-Marchasson I, Rollan Y, Vellas B, et al. Estimated glomerular filtration rate decline and incident frailty in older adults. *Clin J Am Soc Nephrol* 2019;14:1597–1604.

32. Dalrymple LS, Katz R, Rifkin DE, Siscovick D, Newman AB, Fried LF, et al. Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol* 2013;8:2091–2099.

33. Pugh J, Aggett J, Goodland A, et al. Frailty and comorbidity are independent predictors of outcome in patients referred for pre-dialysis education. *Clin Kidney J* 2016;9:324–329.

34. Sam R, Usha A, Kuldeep S, Prichard A, Thomas N, Donovan K, et al. The electronic frailty index (eFI) indicates mortality risk in end stage kidney disease (ESKD) patients on dialysis. *Nephrol Dial Transplant* 2019;34:gfz096.

35. Fitzpatrick J, Sozio SM, Jaar BG, Estrella MM, Segev DL, Parekh RS, et al. Frailty, body composition and the risk of mortality in incident hemodialysis patients: the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease study. *Nephrol Dial Transplant* 2019;34:346–354.

36. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 2012;172:1071–1077.

37. Johansen KL, Delgado C, Bao Y, Tamura MK. Frailty and dialysis initiation. *Semin Dial* 2013;26:690–696.

38. Parker SG, McCue P, Phelps K, McCleod A, Arora S, Nockels K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. *Age Ageing* 2018;47:149–155.

39. Hiramatsu R, Iwagami M, Nitsch D. Association between chronic kidney disease and incident diagnosis of dementia in England: a cohort study in Clinical Practice Research Datalink. *BMJ Open* 2020;10:e033811.

40. Iwagami M, Tomlinson LA, Mansfield KE, Casula A, Caskey FJ, Aitken G, et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. *Nephrol Dial Transplant* 2017;32:142–150.

41. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021. *J Cachexia Sarcopenia Muscle* 2021;12:2259–2261.