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

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Abstract

Background Frailty is characterized by the loss of biological reserves and vulnerability to adverse outcomes. In 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 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 m^2. 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

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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.[1–3] 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.[4,5] 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).

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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 guidelines[26] 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 χ^2 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.

Aims 3 and 4

For the second analysis, time to all-cause mortality and cardiovascular mortality were modelled separately using flexible parametric survival models. Models were stratified by baseline CKD status and included frailty category at index date as an explanatory variable; adjusted models included age, sex, social deprivation, and ethnicity as confounders. Models were stratified by CKD status. Censoring occurred if a patient received dialysis or transplant; the patient transferred out of the practice; the last data collection date for a practice; or, in the outcome of cardiovascular death, death by any other cause occurred. Fine–Gray models were fitted in the CKD patients only with dialysis as the outcome, to adjust for the competing risk of death and dialysis. The adjusted models for all-cause mortality were used to calculate 10 year standardized survival for the CKD compared with no-CKD groups at each frailty level.

Results

Initial sample selection

Of the 1 000 000 patients initially selected, 179 342 were excluded because of ineligible eGFR or having codes for dialysis or transplant prior to index date. After further exclusions for out of practice transfer and mortality prior to index date, a total of 819 893 participants were included: 140 674 had CKD at baseline and 679 219 did not (see flow diagram in *Figure* 1).

Cohort characteristics

In individuals with CKD, the mean age was 77.5 (SD 9.7) years, 38.0% were male, and 97.4% were White. Mean eGFR was 46.1 (SD 9.9) mL/min/1.73 m^2 with the majority in Stage 3a (61.3%); 65.8% of the CKD group had hypertension and 22.5% diabetes. The CKD group were older and more comorbid and had a greater proportion of women and those of White ethnicity than those without CKD ($P < 0.001$) (*Table* 1).

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

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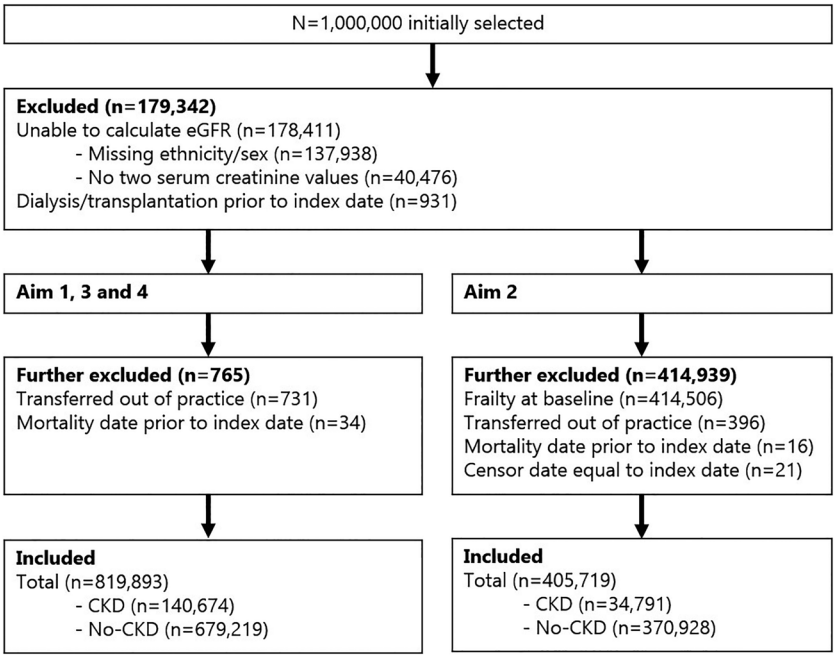

Figure 1 Flow diagram of participants included. Data shown as number (%). Data used to generate figure found in *Table* S2. Aims 1 and 3 explored the prevalence of frailty in the chronic kidney disease (CKD) and no-CKD subject cohorts, and relationship between frailty with all-cause and cardiovascular mortality; Aim 2 investigated the development of frailty in non-frail CKD and non-CKD subject cohorts; and Aim 4 explored the association between frailty level and rates of incident dialysis and kidney transplantation in those with CKD. eGFR, estimated glomerular filtration rate.

deficits contributing to the eFI 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 m^2. 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 = 4731) 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, compared with 4.05 (mild frailty) and 15.01 (severe frailty) in the no-CKD group (*Table* S6). *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; $P < 0.001$),

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Table 1 Overall participant demographics and characteristics

	CKD	No-CKD	*P*-value
N	140 674	679 219	
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%)	
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 m^2)	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%)	
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%)	
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%)	
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 (%).
[a]Comorbidities taken from deficits used to calculate eFI; full deficits can be found in the Supporting Information.
[b]Polypharmacy is defined based on the presence of ≥5 prescribed medications, using Chapters 1–15 of the British National Formulary.

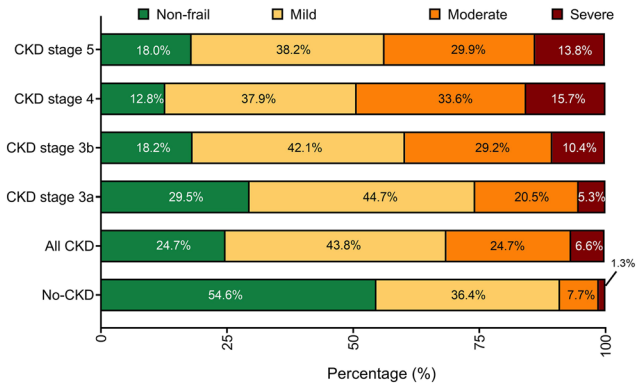

Figure 2 Prevalence of frailty in the chronic kidney disease (CKD) and no-CKD cohorts. Frailty defined using eFI: non-frail (≤4 deficits present); mild frailty (5–8 deficits present); moderate frailty (9–12 deficits present); and severe frailty (≥13 deficits present). Data used to generate figure found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

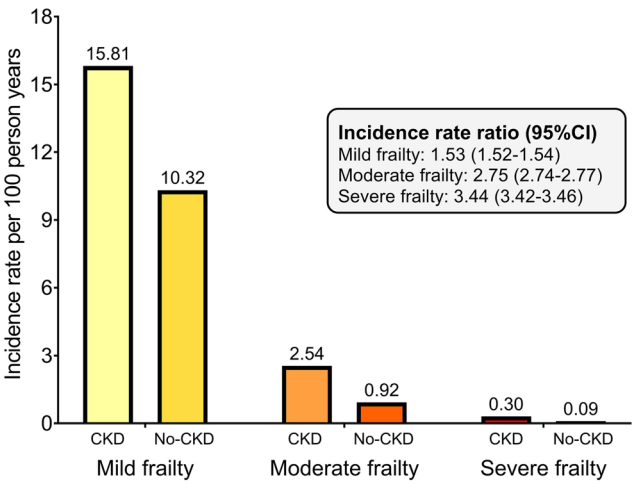

Figure 3 Incidence rate of developing frailty for chronic kidney disease (CKD) and no-CKD groups. Data used to generate figure found in *Table* S5. CI, confidence interval.

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

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Table 2 Frailty and the association with risk of all-cause and cardiovascular mortality in CKD and non-CKD

	CKD		No-CKD	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
All-cause mortality				
Non-frail	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Mild frailty	1.50 (1.47–1.53)	1.22 (1.19–1.24)	1.93 (1.91–1.96)	1.28 (1.26–1.30)
Moderate frailty	2.41 (2.36–2.46)	1.60 (1.56–1.63)	4.19 (4.12–4.25)	1.82 (1.79–1.85)
Severe frailty	3.77 (3.67–3.87)	2.16 (2.11–2.22)	7.49 (7.29–7.69)	2.39 (2.32–2.46)
Cardiovascular mortality				
Non-frail	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Mild frailty	1.64 (1.59–1.68)	1.35 (1.31–1.39)	2.35 (2.30–2.40)	1.49 (1.46–1.52)
Moderate frailty	2.88 (2.80–2.96)	1.96 (1.90–2.02)	5.83 (5.69–5.97)	2.37 (2.31–2.43)
Severe frailty	4.84 (4.67–5.02)	2.91 (2.81–3.02)	11.37 (10.96–11.80)	3.35 (3.22–3.48)

CKD, chronic kidney disease.
Data shown as hazard ratios and upper/lower 95% confidence intervals. All *P*-values <0.001.
[a]Adjusted model for age, sex, social deprivation, and ethnicity.

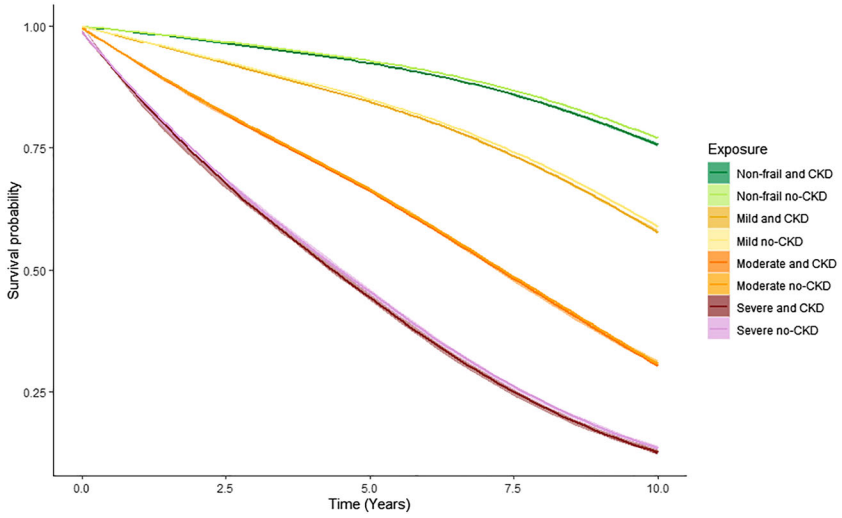

Figure 4 Ten-year survival probability in chronic kidney disease (CKD) and no-CKD groups stratified by frailty at baseline.

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.[28] In the UK, each year, frailty costs £5.8bn, with severe frailty costing an additional £2100 per patient through additional consultations and admissions.[29] 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

Table 3 Frailty and risk of dialysis in those with CKD

	Unadjusted	*P*-value	Adjusted[a]	*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.
[a]Adjusted model for age, sex, social deprivation, CKD stage, and ethnicity.

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 haemodialysis 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 age. 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 m^2 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 m^2 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*.[17] 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 study[33] 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

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Health Cities—Connected Bradford' initiative, which linked data sets from 492 patients undergoing dialysis, showed that the eFI was associated with mortality.[34] 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*.[35]), 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.[36] There are several reasons why frail patients might be initiated on dialysis earlier, including underestimation of kidney function, uraemia, malnutrition, and comorbidity.[37] Frailty has also been associated with faster eGFR decline,[31] which may result in earlier initiation.

The mechanisms that contribute to frailty in CKD are multifaceted[10] and include protein-energy wasting, uraemic toxin accumulation, cognitive impairment, inflammation, inactivity, and anaemia.[10,37] 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,[10] the eFI appears a suitable risk stratification tool that balances practicality and predictive power.

Frailty management

As frailty may be modifiable,[1,14] 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.[3,4] 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[38]) 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].[10] 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,[7] 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.[39] CPRD is characterized by its large coverage, longitudinal follow-up, representativeness, linkages, and data quality processes.[21] Previous study has shown that the CPRD captures most people with decreased kidney function (eGFR $<$ 60 mL/min/1.73 m^2), compared with nationally representative statistics, based on blood test results.[40] 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,[25] and preventative multidimensional interventions should be instigated early to mitigate the development of frailty in this group.

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Conflict of interest

None declared.

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Online supplementary material

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

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