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# Prospective Study of the Association Between Frailty and Health Care Utilization in Patients With Advanced CKD

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**Introduction:** Frailty likely contributes to disproportionate health care utilization among people living with chronic kidney disease (CKD) and undergoing hemodialysis (HD); but this is poorly captured in nephrology clinical and research practice. We examined Fried frailty phenotype among participants with CKD or on HD and explored associations with health care utilization. We examined frailty transitions in relation to hospitalization.

**Methods:** We conducted a prospective observational single-center study of patients with advanced CKD or undergoing HD. Frailty was assessed at baseline, 6 and 12 months. Demographic and clinical data, including comorbid burden, disability, and laboratory parameters were recorded. Data linkage with tertiary hospital captured emergency department (ED) presentations, hospital admissions, and days of hospital stay, excluding admissions for maintenance HD. Negative binomial regression was used to model health care utilization patterns. Frailty progression over study follow-up was described using Cox proportional hazards modelling.

**Results:** Among 256 participants, frailty (36.3%) and prefrailty (46.5%) were highly prevalent. Frailty independently predicted ED presentation (incidence rate ratio [IRR]: 1.25, 95% confidence interval [CI]: 1.09–1.43), hospitalization (IRR: 1.22, 95% CI: 1.08–1.37), and total days of hospitalization (IRR: 1.29, 95% CI: 1.06–1.57) independent of demographics, comorbidity, disability, and inflammation. The median occurrence of hospitalization events was 152 days (interquartile range [IQR]: 44–251) after enrolment, suggesting a window of opportunity where frailty recognition might prompt targeted intervention to prevent frailty-related sequelae. Frailty was highly dynamic; frailty progression was not associated with hospitalization or length of stay.

**Conclusion:** Frailty is a major contributor to excess health care utilization among people with kidney disease. Recognition of the prognostic implications of frailty might allow timely introduction of interventions to improve patient outcomes.

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Frailty is a recognizable clinical syndrome reflecting a decline in physiologic reserve and dysfunction across multiple homeostatic mechanisms resulting in increased vulnerability to acute stressors and adverse health outcomes.[1,2] Among patients with CKD, the pathophysiologic mechanisms of frailty interact with the manifestations of uremia, systemic inflammation, and accelerated cardiovascular disease to produce disproportionately high rates of morbidity and mortality.[3] Frailty prevalence increases with declining kidney function such that rates of frailty among people with advanced CKD and undergoing dialysis are more than double that of community-dwelling adults without CKD, even after adjustment for demographics and multimorbidity.[4–6] The physiologic dysfunction of the frailty syndrome is distinct from chronological aging, impacting patients with CKD at young age, with early studies describing frailty prevalence of 63% in patients aged $< 40$ years at HD initiation.[7] More recent studies report frailty rate of 47.3% in HD populations

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aged < 65 years.[8] Frailty is dynamic and does not progress in a linear fashion, with studies of frailty transitions describing equal rates of frailty progression and remission over longitudinal follow-up in non-CKD and CKD populations alike.[9,10] Frailty is also distinct from comorbidity, although diabetes and peripheral arterial disease are recognized risk factors for frailty in HD populations.[11,12] Finally, frailty is distinguished from disability, because not all individuals living with frailty have impaired activities of daily function, and frailty may not be visible without objective assessment.[13]

Frailty has a unique pathophysiology reflecting the combined impact of accumulation of senescent cells and proinflammatory signaling, conceptualized as "inflammaging."[14] The heightened proinflammatory state characterized by CKD is attributed to uremia and metabolic acidosis, oxidative stress, anemia; comorbid infection further compounds the risk of frailty.[15] Inflammatory markers of particular relevance to CKD states including hypoalbuminemia, elevated ferritin, and c-reactive protein (CRP) frequently accompany frailty in CKD and potentially assist in identifying patients at greater risk of frailty sequelae.[16,17]

Frailty in persons with advanced CKD has prognostic and management implications. A robust body of evidence reflecting a range of study settings and assessment tools has shown that the presence of frailty is associated with a 2 to 5 times increased hazard for all-cause mortality in both CKD and HD populations.[6,18-22] Frailty has been demonstrated to associate with increased rates of ED utilization and hospitalization among patients with CKD or undergoing HD.[7,19,22-26] In turn, hospital admission has been reported to exacerbate frailty.[10] Only a small number of analyses to date, however, have accounted for the impact of frailty on hospitalization independent of the confounding influences of disability, multimorbidity, and inflammation.[21,23] Existing studies have focused primarily on prevalent HD patients and have not examined the impact of frailty on health care utilization patterns among people with CKD. To our knowledge, no existing studies have comprehensively examined the association of frailty with health care contacts, including ED presentations, hospitalization events, and total days of hospital admission independent of the related but separate influences of disability, comorbidity, and inflammation. We hypothesized that frailty accounts for higher rates of health care utilization independent of CKD stage, disability, and comorbidity, including inflammatory state.

The primary goal of this study was to describe the association between Fried frailty phenotype among patients with advanced CKD or with end-stage kidney disease (ESKD) undergoing maintenance HD and health care utilization patterns, adjusting for the confounders of age, disability, comorbidity, and inflammation. We aimed to describe ED presentations, hospitalization events, total days of hospital admission, as well as the use of care models that might alter frailty outcomes, including rehabilitation, specialist geriatric medicine or palliative care involvement, and admission to residential aged care facility (RACF). We aimed to understand how frailty influenced hospital-acquired complications and deterioration and may contribute to care escalation to intensive care unit (ICU) and coronary care unit (CCU). Finally, we examined frailty progression over a follow-up period of 18 months to explore how frailty status transitioned over longitudinal assessment in relation to hospitalization events.

## METHODS

### Study Design

A detailed description of the methodology is reported elsewhere.[27] In brief, this was a prospective, observational longitudinal study from a single tertiary care center in Canberra, Australia, with recruitment taking place between July 2022 and January 2023. Canberra Health Services Department of Renal Medicine is the only publicly funded provider of nephrology care for a source population of 750,000. Ethics approval for this study was provided by Canberra Health Services and Australian National University Human Research Ethics Committee (2020.ETH.00038).

### Study Participants

Study participants were adult patients with advanced CKD defined as estimated glomerular filtration rate < 20 ml/min, or with ESKD undertaking maintenance in-center HD for more than 3 months. Participants were recruited and enrolled sequentially at their attendance for routine nephrology outpatient review and follow-up visits were aligned with ambulatory clinic attendance or HD appointment to mitigate impact of research participation. Exclusion criteria included acute kidney injury, kidney transplantation, medical instability (defined as pulmonary edema or fluid overload with impact on exercise tolerance, symptomatic postural hypotension, symptomatic atrial fibrillation with rapid ventricular response, or as otherwise specified by primary nephrologist), or cognitive impairment threatening informed consent (defined as existing diagnosis of dementia or abbreviated mental test scores of ≤ 5/10 at screening). Participants undertaking home HD or peritoneal dialysis (PD) were excluded from participation because of presumed lower rates of frailty and different

models of clinical care, including an unfavorable clinical environment (specifically an inclined corridor and unsuitable seating) and clinic schedule that did not allow space for frailty assessment aligned with ambulatory clinic attendance. For this observational study, sample size was informed by a number of baseline assumptions, including anticipated rate of frailty of approximately 30% to 40% within our study population, 60% rate of survival of elderly participants undergoing HD at 2 years, and that 70% of predialysis participants with CKD would elect in-center HD modality with minimal ($< 5\%$) anticipated loss to follow-up.[28–30] The source population was an in-center HD population of approximately 150 patients, and 340 patients with advanced CKD regularly attending outpatient appointments. Participants provided informed opt-out consent.

## Frailty Assessment

The key exposure of interest was frailty phenotype as defined by Fried and colleagues, which has been extensively verified in CKD and HD populations.[1,30,31] For the purposes of our study, Fried phenotype was defined by unintentional weight loss $> 5$ kg in the preceding 12 months, physical inactivity defined by the Rapid Assessment of Physical Activity Scale score $\leq 2$ points, self-reported exhaustion based on the Integrated Palliative Care Outcomes Scale-Renal, handgrip weakness defined as grip strength $\geq 1$ SD below the mean referenced to age, sex,[1] and body mass index normative values and slow walk speed, defined as inability to complete 350 m within 6-minute walk test or walk speed $\leq 0.8$ m/s over 10-m walk distance.[32,33] Participants reliant on wheelchair for mobility were not subjected to walk test and were assumed to satisfy the frailty domain of slowness. Frailty was defined by the presence of $\geq 3$ frailty domains, prefrailty was characterized by 1 to 2 criteria and participants were characterized as robust if none of the frailty domains were present. Transitions in frailty phenotype were defined as a move from one phenotype to another on follow-up assessment, for example, prefrailty to frailty. The aggregate frailty score was also calculated as the sum of the component scores (range: 0–5) to allow modelling frailty as a numeric variable within exploratory analyses, as has been done by other groups.[23,34]

Frailty was assessed at each study visit at baseline, 6 months, and 12 months follow-up. Study census date for hospitalization and mortality outcomes was January 31, 2024, or the date of death or kidney transplantation.

[1]Here "sex" is used to denote biological differences between individuals, such as those related to sex chromosomes (like X and Y), sex-specific gene expression, and hormonal variations.

## Clinical and Laboratory Assessments

Comorbidity was defined based on Charlson comorbidity index measured at enrolment based on diagnoses recorded in the electronic medical record. This measure of comorbidity has been validated to predict 10-year survival in persons with multimorbidity based on points allocated for previous myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes with or without end organ damage, hemiplegia, localized solid tumor, leukemia or lymphoma, metastatic tumor, or acquired immunodeficiency syndrome.[35,36] All participants were allocated 2 points based on the presence of moderate or severe CKD.

Additional data collection included demographic details (age, sex, and self-reported ethnicity). Participants provided their fracture history by recall as surrogate marker for falls and CKD-mineral bone disease. Previous studies report that frailty in HD predicted falls and fractures independent of age, sex, comorbidity, and disability, justifying the inclusion of fractures as a relevant confounder.[3,37,38] Laboratory data informing inflammatory status relevant to CKD-frailty pathophysiology, including serum albumin, CRP, and ferritin were collected at baseline and follow-up assessments. For participants undergoing HD, vascular access, dialysis vintage, and dialysis adequacy and urea clearance expressed as most recent Kt/V were recorded at baseline and follow-up visits.

## Disability

Walking and mobility disability were defined based on patient self-report of usual walking aid at baseline or follow-up assessment, classified as nil, single-point stick, or prosthetic limb, 4-wheeled walker, or wheelchair. Participants reported the need for personal assistance with activities of daily living (ADLs), including bathing or showering, dressing, getting in and out of bed or chair, walking, using the toilet, and eating; as well as functional imitation performing instrumental ADLs, including shopping, meal preparation, housekeeping, transportation, managing medications, using the telephone, and managing personal finances.[39]

## Outcomes

Participants were followed-up with from enrolment until January 31, 2024, or censoring event of death or kidney transplant. Health care interaction with tertiary hospital was captured by data linkage, including total number of ED presentations, total discrete hospital admissions after direct admission or interhospital transfer, excluding admissions for maintenance HD and

total days of hospital admission over study follow-up period. International Classification of Diseases, Tenth Revision coding was used to ascertain primary conditions managed during a hospital admission. International Classification of Diseases, Tenth Revision codes describing "age-related physical disability," diagnoses of "awaiting community supports," "prolonged convalescence," "delirium," "dementia," "fall," "malnutrition," "polypharmacy," and "reduced mobility" were considered surrogate frailty diagnoses in line with previous studies that have validated this approach.[40,41] Acuity codes were used to classify acute, maintenance, rehabilitation, and palliative care treatment phases. Admission to RACF was determined from discharge destination and verified by participant report. Cause of death was ascertained from discharge summary and morbidity and mortality review.

### Statistical Analyses

Participant characteristics were described using mean and SD or median and IQR for continuous normally and nonnormally distributed data, respectively; and counts and percentages for categorical data. We compared participant characteristics between patients with CKD or undergoing HD according to baseline frailty phenotype using Mann-Whitney U test and Chi-square tests as appropriate. Time to first admission was described using Kaplan-Meier analysis, compared across Fried phenotypes and CKD stage (CKD vs. HD). For the purposes of exploratory modelling, frailty was treated as a continuous measure scored as 0 to 5 Fried frailty domains. Similar to other groups, we used negative binomial regression models, appropriate to overdispersed count outcome variables, to estimate the association between frailty and the number of ED presentations, hospitalization events, and total days of admission with conversion of the coefficients to IRR.[21,42] The final models for health care utilization events were adjusted for age, sex, stage of CKD (CKD vs. HD), comorbidity, disability, and inflammation. Participants with missing values were excluded from the analysis. The association between frailty progression and health care utilization was examined using Cox proportional hazards regression. Only participants who had undergone $>$ 1 frailty assessment were included in this analysis. Included in the modelling were confounding factors hypothesized to improve frailty outcomes, such as inpatient rehabilitation and geriatrician referral, as well as care models that might be introduced upon clinician recognition of frailty such as admission to RACF and palliative care involvement. Factors associated with a $P < 0.2$ in univariable analysis were included in the multivariable model as per the purposeful model selection method of Hosmer, Lemeshow, and Sturdivant, along with the *a priori* variables of the total number of admissions and total days of hospital admission.[43] The proportional hazards assumption for all models were checked graphically by plotting Schoenfeld residuals and with assessment for multicollinearity. All statistical analyses were carried out using Stata 17.[44] This study is reported in line with Strengthening the Reporting of Observational Studies in Epidemiology guidelines of cohort studies.[45]

## RESULTS

### Patient Characteristics and Frailty Status at Baseline

A total of 256 participants (61.7% male, median age 70.5 years [IQR: 57–80]), including 147 individuals with CKD and 109 individuals with ESKD were recruited to the study, with a high baseline prevalence of frailty and prefrailty (Table 1). A total of 3 patients declined participation at screening, citing competing demands of a chemotherapy regime for active malignancy; one declined further participation following initial frailty assessment, indicating lack of interest in ongoing participation. At screening, 2 participants were excluded because of diagnosis of dementia. Two patients demonstrated acute kidney injury with subsequent recovery and were removed from study follow-up. Among participants with CKD, 7 had identified preference for nondialysis conservative care. Among HD participants 98 (89.9%) were undertaking conventional in-center HD, 8 were undertaking in-center nocturnal therapy, and 3 were doing home-based HD (recruited because of protocol violation but retained in study because of small number). Three patients were excluded from participation based on the presence of cognitive impairment. Six participants were resident in RACF at enrolment. Fracture history was present in 113 of individuals (44.1%). Vascular access and dialysis vintage for the study cohort are reported in Table 1. There was a statistically significant difference in ethnicities represented among participants with CKD compared with those undergoing HD ($P < 0.001$). Persons from Aboriginal and Torres Strait Islander communities, Pasifika, and other minority communities were overrepresented among participants requiring HD.

Both frailty and prefrailty were equally prevalent among participants with CKD and participants undergoing HD ($P = 0.84$). Compared with participants with CKD, participants undergoing HD with frailty or prefrailty were younger, and less comorbid, suggesting a survivor effect. The use of walking aid was common, particularly among participants with frailty or prefrailty and there was no statistically significant difference in use of walking aid by stage of CKD. Fracture

**Table 1.** Demographics at baseline

| Fried Phenotype | Frail 93 (36.3%) | | Prefrail 119 (46.5%) | | Robust 44 (17.2%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| CKD stage | CKD | HD | CKD | HD | CKD | HD | Subtotal CKD | Subtotal HD | Total | *P*-value |
| | 55 (37.4%) | 38 (34.9%) | 66 (44.9%) | 53 (48.6%) | 26 (17.8%) | 18 (16.5%) | 147 | 109 | 256 | NS |
| Age, yrs Median (IQR) | 79 (72–85) | 72 (58–82) | 73 (61–81) | 65 (55–74) | 60.5 (49–72) | 51 (41–58) | 74 (62–82) | 64 (51–75) | 70.5 (57–80) | [a] |
| Sex, *n* (%) male | 26 (47.3%) | 19 (50.0%) | 43 (65.2%) | 38 (71.7%) | 19 (73.1%) | 13 (72.2%) | 88 (59.9%) | 70 (64.2%) | 158 (61.7%) | NS |
| Charleson comorbidity Median (IQR) | 7 (6–9) | 6 (5–8) | 6 (5–8) | 5 (4–7) | 4 (3–6) | 3.5 (3–5) | 6 (5–8) | 5 (4–7) | 6 (4–8) | [a] |
| Usual walking aid | | | | | | | | | | |
| Nil | 17 (30.9%) | 15 (39.5%) | 51 (77.2%) | 44 (83.0%) | 26 (100%) | 18 (100%) | 94 (64.0%) | 77 (70.7%) | 172 (67.2%) | NS |
| SPS | 14 (25.5%) | 8 (21.1%) | 9 (13.6%) | 6 (11.3%) | - | - | 23 (15.7%) | 14 (12.9%) | 36 (14.1%) | |
| 4WW | 20 (36.3%) | 8 (21.1%) | 4 (6.1%) | 1 (1.9%) | - | - | 24 (16.3%) | 9 (8.3%) | 33 (12.9%) | |
| WC | 4 (7.2%) | 7 (18.4%) | 2 (3.1%) | 2 (3.8%) | - | - | 6 (4.1%) | 9 (8.3%) | 15 (5.9%) | |
| ADLs | | | | | | | | | | |
| Personal | 6 (5–6) | 6 (5–6) | 6 (6–6) | 6 (6–6) | 6 (6–6) | 6 (6–6) | 6 (5–6) | 6 (6–6) | 6 (6–6) | ns |
| Instrumental | 5 (3–6) | 5 (2–7) | 5 (7–8) | 7 (6–8) | 8 (7–8) | 8 (7–8) | 6 (5–8) | 7 (4–8) | 6 (5–8) | |
| Resident in aged care facility | | | | | | | 5 (3.4%) | 1 (0.9%) | 6 (2.3%) | |
| Fracture History | 26 (47.3%) | 13 (34.2%) | 30 (45.5%) | 20 (37.7%) | 14 (53.8%) | 10 (55.6%) | 70 (47.6%) | 43 (39.5%) | 113 (44.1%) | NS |
| Ethnicity | | | | | | | | | | |
| ATSI or Pasifika | 8 (8.6%) | | 5 (4.2%) | | 0 (0%) | | 3 (2.0%) | 10 (9.2%) | 13 (5.1%) | [b] |
| Asian | 13 (14.0%) | | 18 (15.1%) | | 9 (20.5%) | | 19 (12.9%) | 21 (19.3%) | 40 (15.6%) | |
| Other | 1 (1.0%) | | 5 (4.2%) | | 1 (2.3%) | | 1 (0.7%) | 6 (5.5%) | 7 (2.7%) | |
| White | 71 (76.3%) | | 91 (76.4%) | | 34 (77.2%) | | 124 (84.3%) | 72 (66.1%) | 196 (76.6%) | |
| Dialysis vintage (days) | 1013.5 (288–2665) | | 844.5 (399.5–1567.5) | | 1108 (476–1680) | | | 873 (342–1845) | | NS |
| Vascular access | | | | | | | | | N = 119 | |
| AV Fistula | | | | | | | | | 86 (72.3%) | |
| AV Graft | | | | | | | | | 8 (6.7%) | |
| Tunneled vascular catheter | | | | | | | | | 25 (21.0%) | |
| Albumin | 39 (36–41) | | 40 (37–42) | | 40.5 (38–43.5) | | | | 39 (36.5–42) | NS |
| Ferritin | 257 (115–580) | | 269 (121–534.5) | | 176 (94.5–3190) | | | | 235 (112–527) | NS |
| C-reactive protein | 5 (2–13.9) | | 3.2 (1.2–7.1) | | 1.8 (0.5–5.8) | | | | 3.6 (1.15–10.1) | NS |

ADL, activity of daily living; AV, arteriovenous; ATSI, Aboriginal or Torres Strait Islander; CKD, chronic kidney disease, HD, hemodialysis; IQR, interquartile range; ns, not statistically significant differences for CKD/Frail versus HD/Frail, CKD/Prefrail versus HD/Prefrail, and CKD/Robust versus HD/Robust using Mann-Whittney U test; NS, not statistically significant differences for CKD/Frail versus HD/Frail, CKD/Prefrail versus HD/Prefrail, and CKD/Robust versus HD/Robust using Chi-square test; SPS, single point stick; WC, wheelchair; 4WW, 4-wheeled walker.

[a]Statistically significant $P<0.05$ for pairwise comparisons for CKD/Frail vs HD/Frail, CKD/Prefrail vs HD/Prefrail and CKD/Robust vs HD/Robust using Mann-Whittney U test.

[b]Statistically significant difference for CKD vs HD using Chi-squared test.

For the purposes of analysis, prosthetic leg ($N = 3$) was categorized as SPS.

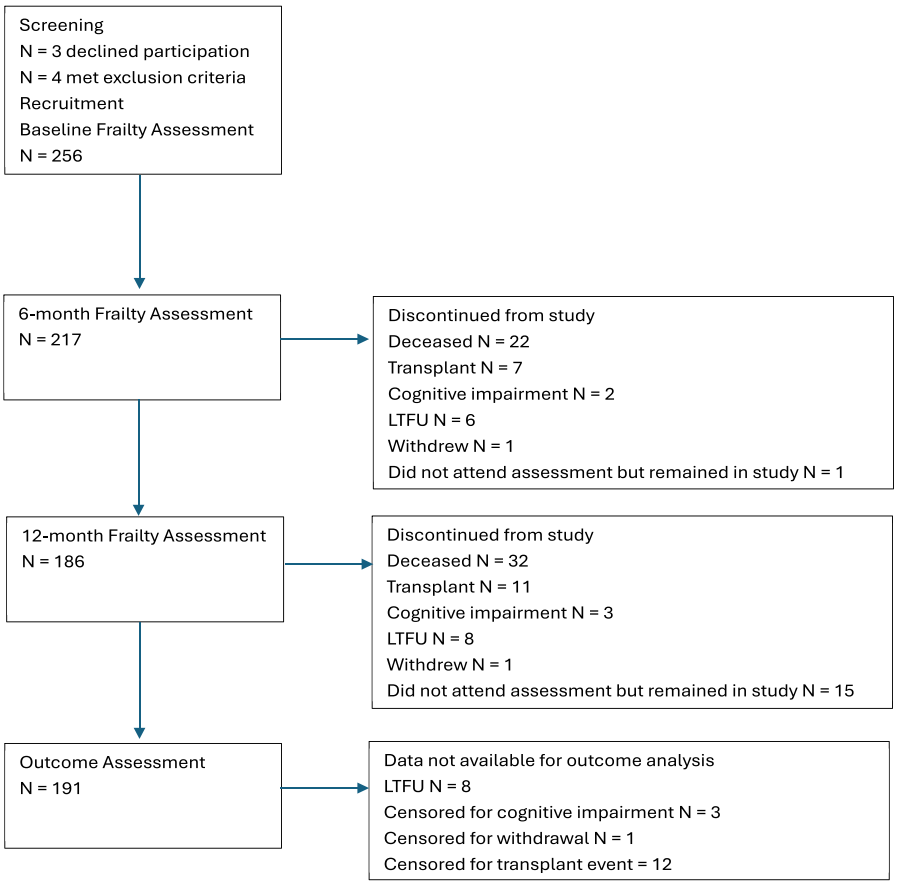


**Figure 1.** Participant flow through study design and longitudinal follow-up. Counts indicate cumulative total for each category at that time point. *Participants marked as "did not attend" maintained their consent for study participation but did not complete further frailty assessments. Their vital status and hospitalization events were collected as per study protocol. LTFU, loss to follow-up where hospitalization events and vital status is unknown.

history did not differ by Fried phenotype or stage of CKD. Median follow-up of the study cohort was 510 days (IQR: 429–541). Over the period of follow-up, 41 participants died and 12 received kidney transplant (Figure 1). A detailed analysis of mortality and kidney transplant outcomes for this study cohort is presented elsewhere.[27] Three participants developed cognitive impairment and were excluded from further participation based on protocol. Eight participants were lost to follow-up, and 1 withdrew consent. Over the course of follow-up, 16 participants progressed from CKD to commence maintenance dialysis. For the purposes of analysis, these individuals were included within the CKD subgroup. Hospitalization data is incomplete for 3 of 256 study participants who transferred to private hospital or regional hospital for rehabilitation, although they remained included in the analysis.

## Health Care Utilization

### *ED Presentations*

There were 517 (241 for CKD, 276 for HD) total ED presentations over the study duration. Frail and prefrail phenotype were associated with statistically significant excess median ED presentations (median: 1.64 [IQR: 0.69–3.98] for frail and 0.75 [IQR: 0.00–2.31] for prefrail) compared with robust phenotype (median: 0.00 [IQR: 0.00–0.85], $P < 0.01$) (Table 2, Figure 2a). ED presentations also occurred more frequently for those participants undergoing HD than those with CKD (Table 3, Figure 3a).

Multivariable modelling examined whether frailty was independently associated with ED presentations, adjusting for the confounders of age, sex, CKD stage, disability, and comorbidity. Model 2 additionally included the confounders of inflammation of ferritin, CRP, and albumin; 41 participants were missing 1 of ferritin, CRP, and albumin, and were not included in this analysis. Frailty score was associated with increased risk of ED presentation with IRR of 1.25 (95% CI: 1.09–1.43, $P = 0.001$) suggesting that for each additional frailty domain, the rate of ED presentation increased by 25%, independent of patient demographics and the confounders of comorbidity, stage of CKD, and disability. This relationship was not modified by age (IRR: 0.99, 95% CI: 0.97–1.00,

**Table 2.** Emergency department and hospitalization patterns by Fried phenotype

| Health care utilization | Frail $n$ = 93 36.3% | Prefrail $n$ = 119 46.5% | Robust $n$ = 44 17.2% | Full cohort $N$ = 256 | $P$-value for difference between groups |
|---|---|---|---|---|---|
| **ED presentations** | | | | | |
| Total | 256 | 225 | 36 | 517 | < 0.01 |
| Median (IQR) | 2 (1–3) | 1 (0–3) | 0 (0–1) | 1 (0–3) | |
| 95% centile range | (0–8) | (0–6) | (0–3) | (0–7) | |
| Rate of ED presentations Median (IQR) | 1.64 (0.69–3.98) | 0.75 (0.00–2.31) | 0 (0.00–0.85) | 0.82 (0–2.34) | < 0.01 |
| **Hospital admissions** | | | | | |
| Total | 336 | 321 | 61 | 718 | < 0.01 |
| Median (IQR) | 2 (1–5) | 2 (0–4) | 1 (0–2) | 2 (1–4) | |
| 95% centile range | (0–13) | (0–11) | (0–4) | (0–10) | |
| Rate of admission per 365 days Median (IQR) | 2.32 (0.80–4.23) | 1.54 (0.00–2.74) | 0.69 (0.00–1.80) | 1.53 (0.64–3.33) | < 0.01 |
| **Days of hospital admission** | | | | | |
| Total | 3076 | 2114 | 108 | 5298 | < 0.01 |
| Median (IQR) | 14 (2–40) | 4 (0–14) | 1 (0–3) | 4 (1–20) | |
| 95% centile range | (0–181) | (0–63) | (0–8) | (0–72) | |

ED, emergency departments; IQR, interquartile range.

$P$ = 0.052). The influence of frailty on excess ED presentations persisted when the inflammatory markers of ferritin, CRP, and albumin were included in the model (Table 4).

### Hospital Admission Events

We observed a total of 718 (336 for CKD, 382 for HD) discreet hospital admission events with 195 (76.2%) study participants experiencing at least 1 hospital

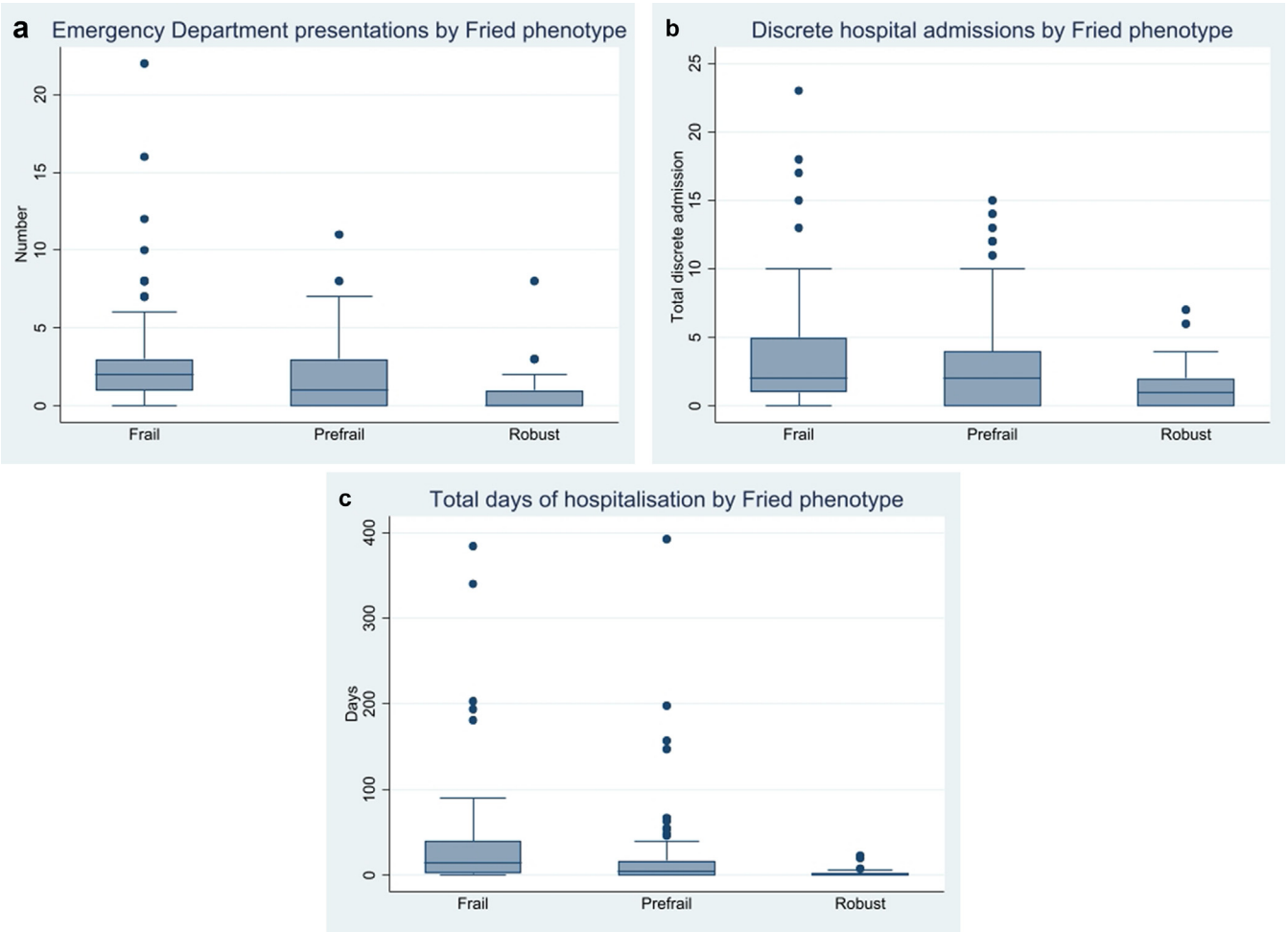


**Figure 2.** (a) Number of emergency department presentations, (b) discrete hospital admissions, and (c) total days of hospitalization by Fried phenotype, where frail $n$ = 93, prefrail $n$ = 119, and robust $n$ = 44. Box and whisker diagram representing median and interquartile range (IQR) (i.e., the "box" 25th percentile–75th percentile) with "whiskers" extending to smallest and largest values within 1.5 times the IQR. Outliers are plotted individually. These differences are statistically significant at $P < 0.05$.

**Table 3.** Emergency department and hospitalization patterns by CKD stage

| Health care utilization | CKD $n = 147$ | HD $n = 109$ | Full cohort $N = 256$ | *P*-value for difference between groups |
|---|---|---|---|---|
| **ED presentations** | | | | |
| Total | 241 | 276 | 517 | 0.04 |
| Median (IQR) | 1 (0–3) | 1 (0–4) | 1 (0–3) | |
| 95% centile range | (0–6) | (0–8) | (0–7) | |
| Rate of ED presentations Median (IQR) | 0.77 (0–2.29) | 0.87 (0–3.37) | 0.82 (0–2.34) | 0.05 |
| **Hospital admissions** | | | | |
| Total | 336 | 382 | 718 | < 0.01 |
| Median (IQR) | 1 (0–3) | 3 (1–4) | 2 (1–4) | |
| 95% centile range | (0–7) | (0–11) | (0–10) | |
| Rate of admission per 365 days Median (IQR) | 0.87 (0–2.82) | 2.00 (0.69–3.61) | 1.53 (0.64–3.33) | 0.01 |
| **Days of hospital admission** | | | | |
| Total | 2365 | 2933 | 5298 | 0.01 |
| Median (IQR) | 3 (0–17) | 8 (1–23) | 4 (1–20) | |
| 95% centile range | (0–61) | (0–147) | (0–72) | |

CKD, chronic kidney disease; ED, emergency departments; IQR, interquartile range.

admission at a median of 194 days (IQR: 82.5–400.5) after enrolment and baseline frailty assessment. Frailty phenotype predicted earlier time to first admission (median: 152 days (IQR: 44–251), $P = 0.0005$) (Figure 4). Frailty was found to be associated with excess hospitalization events, corresponding to a

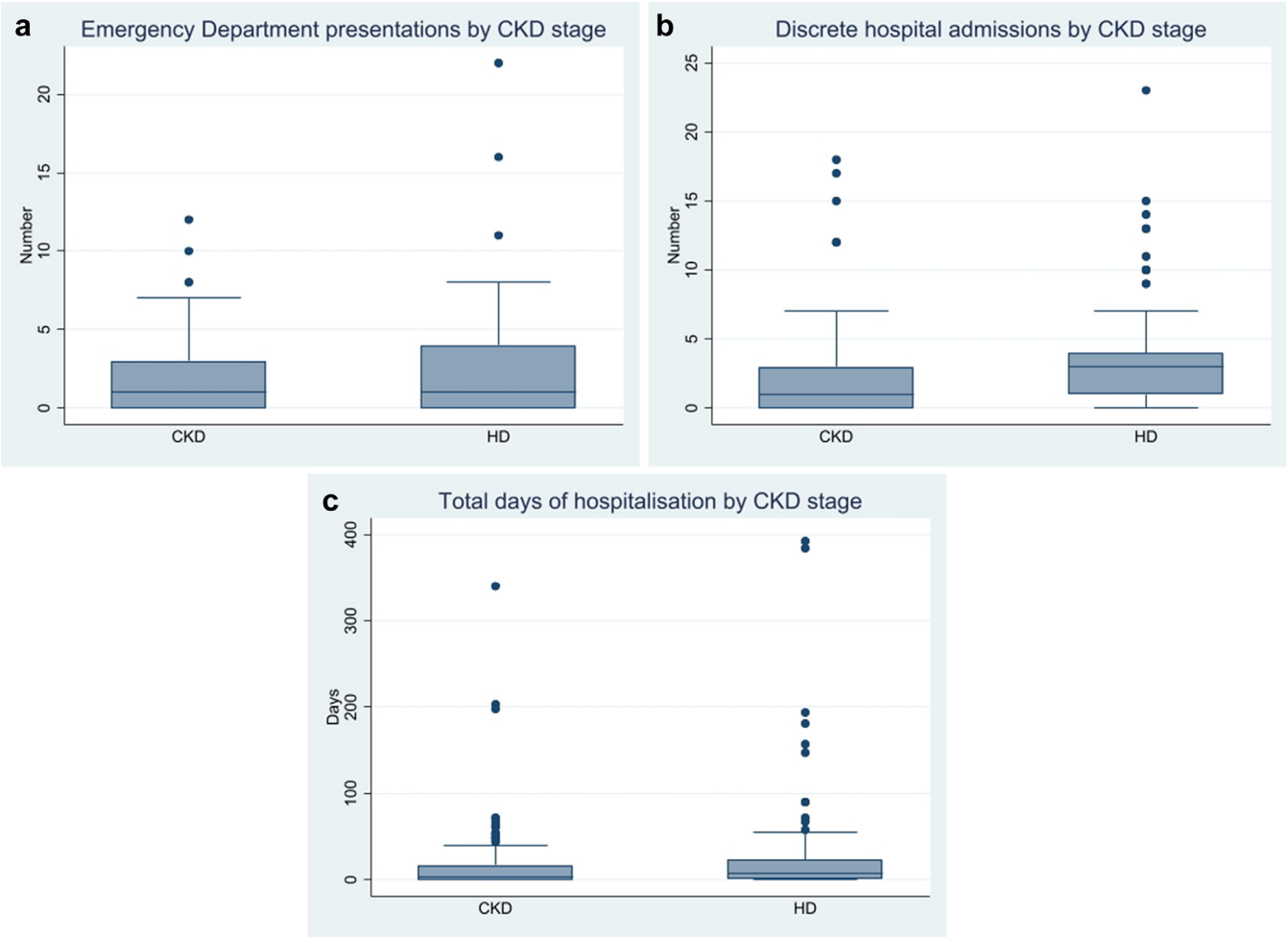


**Figure 3.** (a) Number of emergency department presentations, (b) discrete hospital admissions, and (c) total days of hospitalization by CKD stage, where CKD is $n = 147$ and HD is $n = 109$. Box and whisker diagram representing median and interquartile range (IQR) (i.e., the "box" 25th percentile–75th percentile) with "whiskers" extending to smallest and largest values within 1.5 times the IQR. Outliers are plotted individually. These differences are not statistically significant. CKD, chronic kidney disease.

**Table 4.** Multivariable modelling: emergency department presentations

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| Variable | IRR | 95% CI | *P*-value | IRR | 95% CI | *P*-value |
| Frailty score | 1.25 | 1.09–1.43 | 0.001 | 1.24 | 1.07–1.43 | 0.004 |
| Age | 0.99 | 0.97–1.00 | 0.052 | 0.98 | 0.97–1.00 | 0.045 |
| Sex | 1.37 | 1.00–1.89 | 0.052 | 1.35 | 0.96–1.89 | 0.081 |
| CKD stage | 1.43 | 1.06–1.93 | 0.020 | 1.40 | 0.95–2.04 | 0.086 |
| Comorbidity | 1.12 | 1.02–1.22 | 0.017 | 1.14 | 1.04–1.26 | 0.006 |
| Usual walking aid | 1.00 | 0.81–1.24 | 0.968 | 1.01 | 0.81–1.27 | 0.904 |
| ADLs | 0.93 | 0.78–1.09 | 0.362 | 0.91 | 0.77–1.09 | 0.320 |
| iADLs | 0.98 | 0.90–1.07 | 0.619 | 0.98 | 0.90–1.07 | 0.686 |
| Ferritin | | | | 1.00 | 0.99–1.00 | 0.132 |
| CRP | | | | 1.00 | 0.99–1.01 | 0.899 |
| Albumin | | | | 1.03 | 0.99–1.07 | 0.534 |

ADLs, activities of daily living; CKD, chronic kidney disease; CI, confidence interval; CRP, c-reactive protein; iADLs, instrumental ALDs; IRR, incidence rate ratio.

median rate of admission per 365 study days of 2.32 (IQR: 0.80–4.23) and 1.54 (IQR: 0–2.74), for participants with frailty and prefrailty, respectively, compared with robust phenotype (0.69 [IQR: 0.00–1.84]). These differences were statistically significant, corresponding to $P < 0.01$ (Table 2, Figure 2b). ESKD and the need for HD were associated with additional hospital admission events compared with advanced CKD not requiring dialysis (Table 3, Figure 3b).

Multivariable modelling demonstrated that frailty was associated with increased risk of hospital admission events independent of age, sex, comorbidity, and disability (IRR: 1.22, 95% CI: 1.08–1.37, $P = 0.001$). This relationship persisted after adjusting for inflammation (Table 5).

### *Total Days of Hospitalization*

Total days of hospital admission across the study cohort totaled 5298 days, with the longest length of stay being 392 days. Median number of days of hospital admission was 4 days (IQR: 1–20) for the total study cohort. Fried phenotype was found to align with extended days of hospital admission; frailty was associated with a median of 14 days (IQR: 2–40) and prefrailty associated with a median of 4 days (IQR: 0–14), compared with robust phenotype, which demonstrated a median of 1 day (IQR: 0–3) (Table 2, Figure 2c). These differences were all statistically significant ($P < 0.01$). Reliance on HD was similarly accompanied by significantly more days of hospital admission with a median of 3 (IQR: 0–17) days for CKD and 8 (IQR: 1–23) days for HD ($P = 0.01$) (Table 3 and Figure 3c).

Multivariable modelling revealed that frailty was accompanied by increased total days of hospitalization, corresponding to 29% increased duration of hospitalization for every frailty domain present (IRR: 1.29, 95% CI: 1.06–1.57, $P = 0.011$) (Table 6). Although modified by comorbidity, dependence on walking aid, and impairment in personal ADLs, frailty was associated with excess days of hospitalization independent of age, sex, and stage of CKD. The relationship between total days of hospitalization and frailty persisted after adjusting for inflammation.

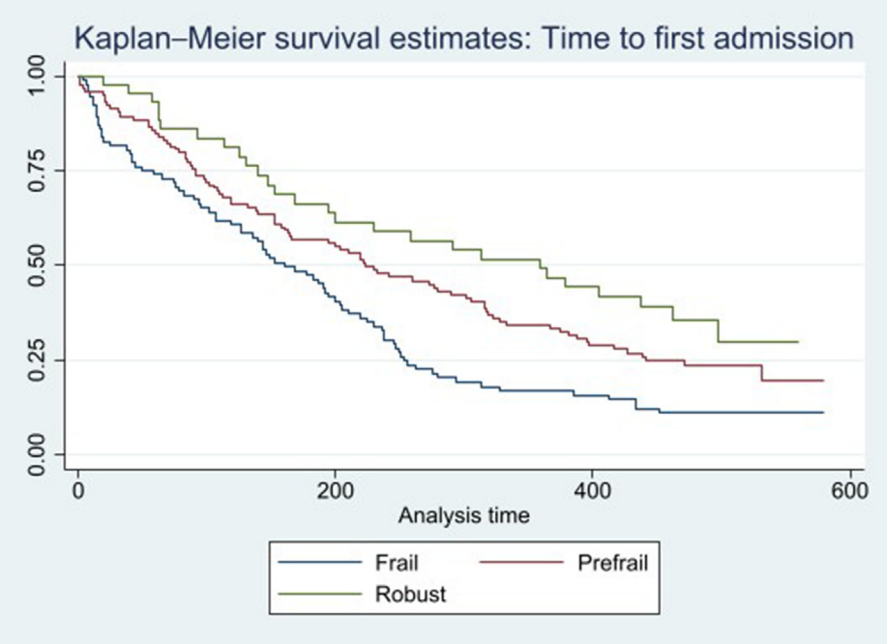


**Figure 4.** Time to first hospital admission in days compared between Fried frailty phenotypes. The impact of frailty on time to first hospital admission was evaluated through Kaplan-Meier analysis with log rank test of $P = 0.0005$. Across the total study cohort, hospital admission occurred at a median of 194 days (IQR: 82.5–400.5). The median time to admission was 152 days (IQR: 44–251) for participants with frailty, compared to 219 days (IQR: 88–412) for participants with prefrailty, and 302 days (IQR: 119–463) for participants with robust phenotype.

**Table 5.** Multivariable modelling: Hospital admissions

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| Variable | IRR | 95% CI | *P*-value | IRR | 95% CI | *P*-value |
| Frailty score | 1.22 | 1.08–1.37 | 0.001 | 1.16 | 1.02–1.31 | 0.021 |
| Age | 0.99 | 0.98–1.00 | 0.132 | 0.99 | 0.97–1.00 | 0.131 |
| Sex | 1.42 | 1.06–1.91 | 0.017 | 1.39 | 1.02–1.90 | 0.037 |
| CKD stage | 1.49 | 1.31–1.96 | 0.004 | 1.40 | 1.00–1.98 | 0.052 |
| Comorbidity | 1.10 | 1.01–1.19 | 0.031 | 1.12 | 1.02–1.22 | 0.015 |
| Usual walking aid | 1.06 | 0.88–1.28 | 0.512 | 1.16 | 0.94–1.42 | 0.162 |
| ADLs | 0.87 | 0.74–1.03 | 0.116 | 0.85 | 0.71–1.02 | 0.083 |
| iADLs | 1.03 | 0.95–1.11 | 0.524 | 1.06 | 0.97–1.16 | 0.170 |
| Ferritin | | | | 1.00 | 0.99–1.00 | 0.218 |
| CRP | | | | 1.00 | 0.99–1.01 | 0.450 |
| Albumin | | | | 1.00 | 0.96–1.04 | 0.904 |

ADLs, activities of daily living; CKD, chronic kidney disease; CI, confidence interval; CRP, c-reactive protein; iADLs, instrumental ALDs; IRR, incidence rate ratio.

### *Additional Metrics of Health Care Utilization*

On longitudinal follow-up of the study cohort, there were 13 new admissions to RACF, 20 new fracture events, 27 referrals to specialist palliative care services, 16 episodes of inpatient rehabilitation, and 7 admissions for specialist geriatric care among participants with frail and prefrail phenotypes. No patients of robust phenotype were referred for use of these services.

**Patterns of Care Escalation: Use of ICU and CCU.** Within the study cohort, there were 35 admissions to ICU; 34 of these were among participants with frailty or prefrailty. There was 1 participant with robust phenotype who was admitted to the ICU with COVID-pneumonitis and pericarditis. A total of 12 participants with frailty and prefrailty were admitted to CCU. An additional CCU admission occurred for 1 participant with robust phenotype.

## Frailty Progression Over Longitudinal Follow-Up

We examined whether hospital admission events and days of hospitalization were associated with progression of frailty. A total of 216 participants attended >1 frailty assessment. Of these, 68 (31.4%) demonstrated progression of frailty either from robust to prefrailty, prefrailty to frailty, or robust to frailty. In contrast, just 16 participants progressed from CKD to ESKD. Included in the modelling to explore frailty progression were factors hypothesized to improve frailty outcomes such as inpatient rehabilitation and geriatrician referral, as well as care models that might be introduced upon clinician recognition of frailty such as admission to RACF and palliative care involvement. Univariable analysis revealed that age, CKD stage, comorbidity, disability in ADLs or instrumental ADLS, admission to RACF, referral to specialist geriatric care or rehabilitation, and fracture were not associated with frailty progression; these variables were dropped from multivariable analysis. In contrast, univariable analysis indicated that sex, usual walking aid, and referral to specialist palliative care were associated with frailty progression. These variables were included in the Cox proportional hazards multivariable model along with *a priori* variables, including total number of hospital admissions and total days of hospitalization. We were unable to identify any variables associated with frailty progression (Table S1).

**Table 6.** Multivariable modelling: total days of hospitalization

| | Model 1 | | | Model 2 | | |
|---|---|---|---|---|---|---|
| Variable | IRR | 95% CI | *P*-value | IRR | 95% CI | *P*-value |
| Frailty score | 1.29 | 1.06–1.57 | 0.011 | 1.28 | 1.03–1.59 | 0.025 |
| Age | 0.99 | 0.98–1.01 | 0.546 | 0.99 | 0.97–1.01 | 0.289 |
| Sex | 1.31 | 0.85–2.04 | 0.225 | 1.22 | 0.76–1.97 | 0.412 |
| CKD stage | 1.44 | 0.94–2.20 | 0.098 | 1.53 | 0.91–2.56 | 0.106 |
| Comorbidity | 1.18 | 1.03–1.35 | 0.018 | 1.19 | 1.04–1.37 | 0.011 |
| Usual walking aid | 1.41 | 1.06–1.88 | 0.020 | 1.47 | 1.10–1.99 | 0.010 |
| ADLs | 0.74 | 0.56–0.99 | 0.041 | 0.72 | 0.54–0.95 | 0.020 |
| iADLs | 0.98 | 0.87–1.11 | 0.732 | 1.02 | 0.90–1.16 | 0.746 |
| Ferritin | | | | 1.00 | 0.99–1.00 | 0.119 |
| CRP | | | | 1.00 | 0.99–1.01 | 0.831 |
| Albumin | | | | 0.99 | 0.94–1.05 | 0.867 |

ADLs, activities of daily living; CKD, chronic kidney disease; CI, confidence interval; CRP, c-reactive protein; iADLs, instrumental ALDs; IRR, incidence rate ratio.

## Cause of Hospital Admissions and Cause of Death

Among 718 discrete admissions, there were a total 745 admission and complication diagnoses, reflecting dual pathology in some admissions. The leading causes of admission are described in Table S2. In addition, there were 28 elective admissions for vascular access creation, approximately equally distributed among participants with CKD ($n = 17$) and undergoing HD ($n = 11$). Participants with frailty and prefrailty were at increased risk of admission for all conditions but were particularly disproportionately so for admissions for infectious illness, vascular access complication, and surrogate frailty conditions (Figure 5). When comparing stage of CKD, participants with CKD were more likely to be admitted for iron deficiency anemia, elective dialysis access placement, musculoskeletal complaint, type 2 diabetes complications, or urological issues than their HD counterparts; whereas participants dependent on HD were more likely to be admitted for hypotension, peripheral arterial disease, or vascular access complication ($P < 0.01$). Participants with advanced CKD or HD reliance were equally likely to experience admission for infection, frailty surrogate, major adverse cardiac events, or renal complication.

There were a total of 41 deaths during the study follow-up period, including 7 deaths among participants who chose to withdraw from dialysis (17%, representing 35% of dialysis-related deaths) and 14

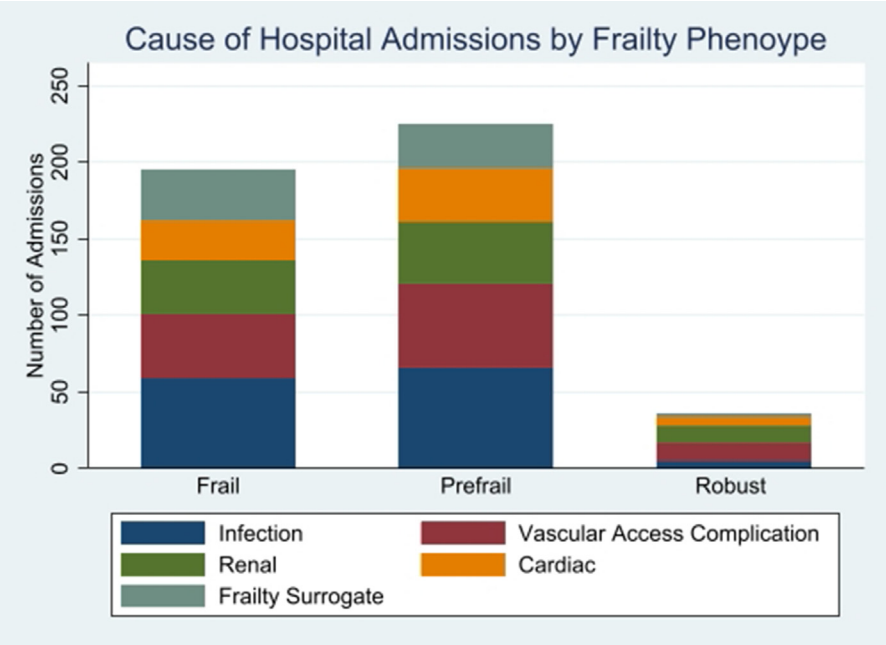


**Figure 5.** Leading cause of admission by Fried phenotype.

deaths following ICU or CCU admission (34%). Causes of death are described in Table S3.

## DISCUSSION

Frailty is a state of accelerated aging characterized by reduced reserve and increased vulnerability to acute physiological stressors, along with the risk of adverse patient outcomes, including disability, hospitalization, and death.[2,46] Despite the burden of frailty on individuals and health systems, frailty is inconsistently measured and managed in nephrology care models. Clinical recognition of frailty within CKD populations is likewise inconsistent, with no clear consensus on the most appropriate frailty metric. Operationalized definitions must distinguish frailty from the related phenomena of sarcopenia, disability and comorbidity, which act as risk factors for, but distinct entities from the frailty construct. Two recent scoping reviews report up to 40 heterogenous frailty assessment tools among patients with kidney disease but favor the use of the Fried frailty phenotype for its clinical utility, construct validity, and criterion validity in nephrology populations.[13,30,47] Differences in frailty metrics as well as study population characteristics such as age, comorbidity, and stage of CKD account for substantial variation in reported frailty prevalence and outcomes. Although initially described among older patients, frailty in the context of CKD and particularly among HD populations occurs at young age and demands the use of frailty assessment tools that are validated in younger people. Within the current literature, the Fried frailty phenotype is emerging as the common metric for frailty assessment within nephrology populations.[30,47,48] In the present study, our choice of Fried frailty phenotype was informed by the need to assess frailty across the range of patient demographics, in particular participants aged $<$ 65 years; and to distinguish frailty from the confounding impacts of disability and comorbidity. Specific to our research question, the Fried frailty phenotype allowed the description of a prefrail state to permit the examination of frailty dynamics over longitudinal follow-up. Alternative frailty assessment tools include Rockwood's Clinical Frailty Scale, which relies heavily on descriptions of disability and functional impairment, and in our research context was felt to be insufficiently sensitive to allow examination of frailty dynamics.[49–51] Similarly, the Fried phenotype was preferred to the Frailty Index, which conceptualizes frailty as an accumulation of deficits and disability states, which has not been extensively used or validated among advanced CKD and HD populations.[52] Importantly, neither Rockwood's Clinical Frailty Scale nor Frailty Index are validated for use among younger people.

In this longitudinal examination of patients with advanced CKD and ESKD, we report high prevalence of Fried phenotype frailty and prefrailty and provide a detailed description of the implications for hospitalization and health care utilization. We found that frailty and prefrailty are independent risk factors for ED presentation, earlier hospital admission, excess hospital admission events, and extended days of hospitalization, with each additional frailty domain increasing the odds of excess health care utilization. Frailty outperformed

age, stage of CKD, comorbidity, disability, and inflammation in its association with key health care outcomes, suggesting that it might be the unmeasured confounder in the earlier published literature highlighting high health care utilization patterns among this patient population. Other studies have similarly described a high rate of health care utilization among people living with advanced CKD and undergoing HD. Our observed rate of ED presentations, length of stay, and requirement for RACF placement aligns closely with that described by Tonelli and colleagues who recently reported that patients cared for by nephrologists were characterized by greater comorbidity, polypharmacy, hospitalization events, and probability of long-term care placement compared with any other patient group.[53] This study of >2 million patients registered with the Canadian Alberta Health database reports a mean of 1.7 ED visits (95% CI: 1.7–1.7) and of 11.1 days/yr of patient follow-up spent in hospital (95% CI: 11.0–11.1), but did not account for the impact of frailty in its analyses. Other studies set in West Bengal, India report similarly extended hospital length of stay in HD patients, describing a mean number of days of hospitalization of 10.31 (SD: 6.07 days) over 365 days of study follow-up, again without exploring frailty as an etiological factor.[54] These figures compared closely with the present study wherein we found a median rate of ED presentation of 1.64 (IQR: 0.69–3.98) days and median days of hospitalization of 14 days (IQR: 2–40) per 365 days among patients with frailty. This speaks to the need for frailty assessment within clinical, administrative, and research activity to best understand the impact of frailty. Previous studies have described frailty alongside ED and hospitalization use patterns, focusing on prevalent HD populations, but have failed to account for the confounding interactions of comorbidity and disability.[7,22,24,25] Nevertheless, a picture of high health care utilization emerges. The McAdams-DeMarco group from Baltimore, MD, USA quantified the number of hospitalization events and explored the relationship with Fried frailty status independent of comorbidity and disability with a mean follow-up period of 3 years. They reported that frailty was associated with a 1.43-fold greater (95% CI: 1.00–2.03, $P = 0.049$) number of hospitalization events independent of age, sex, comorbidity, and disability.[23] This effect size corresponds to our findings, wherein each Fried frailty domain contributes increased risk of hospitalization of 22% (IRR: 1.22, 95% CI: 1.08–1.39, $P = 0.001$). Similarly, Garcia-Canton's examination of prevalent HD patients in Spain using the Edmonton Frail Scale reports a similar impact on hospital length of stay for patients with frailty at 11.8; and substantially increased rate of hospitalization (IRR: 1.78, 95% CI: 1.15–2.77, $P = 0.0094$), independent of disability and comorbidity.[21] Taken together, these data reveal that frailty's impact on health care utilization patterns among patients undergoing HD is a universal phenomenon, contributing to health care system demand worldwide.

Our analysis is unique for its inclusion of patients with predialysis CKD. We demonstrate that health care demand was indeed greater among patients with ESKD dependent on HD, but that presence of frailty in advanced CKD was also associated with excess ED presentations, hospitalization events, and total days of hospital admission.

This finding corresponds with recent report from Taiwan wherein every 1-point Fried frailty point was found to increase risk of unexpected ED visit (hazard ratio: 1.20, 95% CI: 1.03–1.39, $P < 0.05$) and hospitalization (hazard ratio: 1.24, 95% CI: 1.06–1.46, $P < 0.05$) among patients with CKD stages 3 to 5.[26] To our knowledge, ours it the first study to link frailty with high acuity contact with health care systems among patients with both advanced CKD and ESKD undergoing HD. Although excluded from our study, it is likely that this relationship exists among patients undergoing PD too; however, the only studies to examine this date have relied on an in-house frailty questionnaire that has not been externally validated.[55,56]

Although a detailed health economic analysis is beyond the scope of this work, the previously invisible cost of frailty emerges as a public health priority for health care executives and policymakers. In our Australian study setting, health care expenditure related to CKD is substantial, with 1.2% of the allocated expenditure in Australian health care attributed to CKD management, predominantly public hospital admissions.[57] We speculate that frailty likely contributes to this phenomenon but poorly captured by current clinical, research, and database reporting. In US settings, the ACTIVE/ADIPOSE study leveraged data linkage available through the US Renal Data System and Medicare claims and found that frail individuals incurred 22% (95% CI: 9.6%–35.8%) higher costs than nonfrail individuals, primarily driven by higher inpatient expenditures.[58]

Our study critically demonstrates the utility for incorporating validated frailty assessment into routine nephrology care. In this opt-out model of consent, Fried-based frailty assessment was found to be acceptable to participants when combined with routine outpatient attendance, where weight parameters are regularly assessed, and fatigue or low energy may be triangulated from patient-reported symptom assessment tools in routine use in many settings.

Furthermore, we found that hospital admission followed at a median of 152 days (IQR: 44–251) after enrolment and initial assessment confirming frailty, suggesting a window of opportunity in which frailty recognition might be followed by targeted intervention to prevent hospitalization and other frailty-related sequelae. Our observational data reveal low rates of inpatient rehabilitation, specialist geriatric care, and palliative care referral. Underutilization of rehabilitation care models have previously been described for nephrology populations, with studies reporting barriers to cardiac rehabilitation referral and access despite equivalent efficacy and cost-effectiveness.[59,60] Inpatient physical rehabilitation is similarly underutilized and appears to be less impactful in patients undergoing HD.[61,62] Furthermore, patients with ESKD are less likely to be referred to specialist palliative care services or receive late referral for end of life care.[63] We hypothesize that poor recognition of frailty and its clinical implications contribute to inequitable access to existing health care models that might arguably improve frailty outcomes. We also observed a greater proportion of ethnic diversity among patients with ESKD undergoing HD, revealing health care inequities among marginalized and minority patients from culturally and linguistically diverse communities. The interactions between ethnicity, culture and frailty deserve further examination to ensure that the impact of frailty does not further compound existing systemic inequities.

Infection, renal causes, and cardiac events were primarily contributary to the cause of death for most participants with mortality event. Moreover, unsuccessful care escalation and elective dialysis withdrawal were commonplace. We report a 35% rate of dialysis withdrawal, in line with international data registries, where frailty is poorly captured as a potential explanatory variable.[64,65] Our data strengthen a limited number of studies to date, which suggest that frailty increases odds of dialysis withdrawal.[66,67] We provide evidence to support existing qualitative descriptions of the contributory impact of long and frequent hospital admissions, unresolved symptoms, and intolerable treatment burden.[66,68] These data emphasize the urgent need for frailty assessment in both nephrology clinical practice and capture within database registries. Recognition of the prognostic implications of frailty might allow timely introduction of care scaffolding, advanced communication practices, and integration of palliative care services and as well as offering granular understanding of patient outcomes and health services planning following database reports.

This study is novel for its description of frailty transitions and the dynamic nature of frailty. We identified a high rate of frailty progression; indeed, participants were more likely to demonstrate deterioration in frailty state than to commence dialysis for ESKD. Unlike earlier studies, however, our analysis was unable to identify any health care utilization patterns associated with frailty progression, with neither hospitalization event nor total days of hospital admission demonstrating a significant impact.[10] The greater clinical need, however, is to understand the factors associated with frailty remission in this patient population. Recent study using the Fried frailty assessment described improved mortality and hospitalization outcomes following observed improvements in frailty phenotype in participants undergoing HD in Canada.[69] These data support the need to further explore frailty interventions at the advanced CKD stage, before the onset of ESKD and the additional demands of dialysis. The dynamic nature of frailty suggests potential for successful frailty intervention when designed with this patient population in mind.[27,70]

Among our study's strengths are the high degree of data completeness in a high complexity tertiary hospital setting. This is afforded by the opt-out consent strategy and unique setting of the only publicly funded provider of nephrology and dialysis care to a large metropolitan and regional area, galvanized by a single electronic medical record.

Study limitations include the single-center setting and focus on frailty assessments based in an ambulatory care outpatient setting, where the most frail participants might be too immobile to attend clinic and thus missed by this recruitment strategy. This study is hospital-centric in its lens and cannot account for or quantify interactions with community-based health care providers, including primary care, community care or volunteer organizations. Our findings may be impacted by survivor bias in advanced CKD and HD; further studies are needed to evaluate frailty's impact on health care utilization patterns at earlier stages of CKD. Our study protocol excluded patients undertaking PD from participation. Certain myths about the safety of exercise and physical activity persist within the nephrology community and appear particularly difficult to expel from PD care, where patients may be discouraged from participation because of perceived barriers (catheter healing, dressing and water, intraabdominal pressure, and hernias).[71] The International Society for Peritoneal Dialysis has published recommendations for physical activity and exercise which specifically promote the use of appropriate frailty screening tools including Fried phenotype physical assessment, among other tools, to assist in targeting frailty interventions to patients receiving PD.[72] Future evaluations of frailty within nephrology populations must include patients receiving PD. Finally, our data analysis and, in particular,

diagnostic and acuity codes rely heavily on the accuracy of administrative data. This has been done in other settings, including use of administrative claims and electronic health records among US Veterans, as well as within the National Health Service using the Hospital Episode Statistics, and within the Taiwanese National Health Insurance based on International Classification of Diseases, Tenth Revision codes, all in the examination of frailty and adverse clinical outcomes.[73,74] To the best of our knowledge, this is the first Australian study to leverage administrative coding to provide this comprehensive study of frailty sequelae among patients with advanced CKD and ESKD.

## CONCLUSION

Frailty in the context of advanced CKD and ESKD adds significantly to health care utilization patterns. We confirm the utility of frailty assessment in the nephrology outpatient setting and distinguish the impact of frailty from the related but separate burdens of disability, comorbidity, and inflammation. We highlight the window of opportunity for frailty intervention following outpatient assessment using validated frailty assessment tool. Assessment for frailty permits the prediction of adverse clinical outcomes and high-acuity contact with health care systems, including excess ED presentations, hospital admission and frequent readmission, days of hospitalization, and clinical deterioration with ICU or CCU involvement as well as dialysis withdrawal. There is an urgent need to increase frailty assessment and recognition to promote shared decision-making, uphold high-value care practices, and allow better allocation of health care resources toward evidence-based interventions aimed at mitigating frailty and its sequelae.

## DISCLOSURE

All the authors declared no competing interests.

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## DATA AVAILABILITY STATEMENT

Deidentified data may be provided upon reasonable request to the corresponding author.

## AUTHOR CONTRIBUTIONS

ALK designed the study protocol, authored the ethics applications, and received funding to support the research activity. AK recruited and assessed participants, analyzed the data, and authored the manuscript. AMR provided support for statistical methodology and analysis, draft revision and approval for the final version for submission. SR provided methodological guidance, made substantial contributions to analysis and data interpretation, and provided draft revision and approval for the final version for submission. KLH recruited and assessed participants. NJG provided methodological guidance, made substantial contributions to the concept and design of the article, analysis and data interpretation, and provided draft revision and approval for the final version for submission. KLP provided protocol advice, draft revision and approval for the final version for submission. AMD provided protocol advice, draft revision, and approval for the final version for submission. GST made substantial contributions to the concept and design of the protocol, data extraction, analysis and data interpretation, and offered structural and content revision as well as approval for the final version for submission.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Frailty progression univariable and multivariable analysis.

**Table S2.** Descriptive analysis of cause of admission.

**Table S3.** Cause of death.

## REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. https://doi.org/10.1093/gerona/56.3.m146
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762. https://doi.org/10.1016/S0140-6736(12)62167-9
3. McAdams-DeMarco MA, Suresh S, Law A, et al. Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. *BMC Nephrol*. 2013;14:224. https://doi.org/10.1186/1471-2369-14-224
4. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kidney Dis Off J Natl Kidney Found*. 2004;43:861–867. https://doi.org/10.1053/j.ajkd.2003.12.049
5. Roshanravan B, Khatri M, Robinson-Cohen C, et al. A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis Off J Natl Kidney Found*. 2012;60:912–921. https://doi.org/10.1053/j.ajkd.2012.05.017

6. Wilhelm-Leen ER, Hall YN, Tamura MK, Chertow GM. Frailty and chronic kidney disease: the Third National Health and Nutrition Evaluation Survey. *Am J Med*. 2009;122:664–671.e2. https://doi.org/10.1016/j.amjmed.2009.01.026
7. 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. https://doi.org/10.1001/archinternmed.2012.3020
8. Chu NM, Chen X, Norman SP, et al. Frailty prevalence in younger end-stage kidney disease patients undergoing dialysis and transplantation. *Am J Nephrol*. 2020;51:501–510. https://doi.org/10.1159/000508576
9. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. *Arch Intern Med*. 2006;166:418–423. https://doi.org/10.1001/archinte.166.4.418
10. Johansen KL, Dalrymple LS, Delgado C, et al. Factors associated with frailty and its trajectory among patients on hemodialysis. *Clin J Am Soc Nephrol CJASN*. 2017;12:1100–1108. https://doi.org/10.2215/CJN.12131116
11. Okuyama M, Takeuchi H, Uchida HA, et al. Peripheral artery disease is associated with frailty in chronic hemodialysis patients. *Vascular*. 2018;26:425–431. https://doi.org/10.1177/1708538118756690
12. Kakio Y, Uchida HA, Takeuchi H, et al. Diabetic nephropathy is associated with frailty in patients with chronic hemodialysis. *Geriatr Gerontol Int*. 2018;18:1597–1602. https://doi.org/10.1111/ggi.13534
13. Nair D, Liu CK, Raslan R, McAdams-DeMarco M, Hall RK. Frailty in kidney disease: A comprehensive review to advance its clinical and research applications. *Am J Kidney Dis*. 2024. https://doi.org/10.1053/j.ajkd.2024.04.018
14. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018;15:505–522. https://doi.org/10.1038/s41569-018-0064-2
15. Hanna RM, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. *Blood Purif*. 2020;49:202–211. https://doi.org/10.1159/000504240
16. Kaysen GA. Biochemistry and biomarkers of inflamed patients: why look, what to assess. *Clin J Am Soc Nephrol*. 2009;4:S56–S63. https://doi.org/10.2215/CJN.03090509
17. Kaysen GA, Dubin JA, Muller HG, et al. Inflammation and reduced albumin synthesis associated with stable decline in serum albumin in hemodialysis patients. *Kidney Int*. 2004;65:1408–1415. https://doi.org/10.1111/j.1523-1755.2004.00520.x
18. Ali H, Abdelaziz T, Abdelaal F, Baharani J. Assessment of prevalence and clinical outcome of frailty in an elderly predialysis cohort using simple tools. *Saudi J Kidney Dis Transplant*. 2018;29:63–70. https://doi.org/10.4103/1319-2442.225175
19. Vezza C, Vettoretti S, Caldiroli L, Bergamaschini L, Messa P, Cesari M. Use of the frailty index in older persons with chronic kidney disease. *J Am Med Dir Assoc*. 2019;20:1179–1180. https://doi.org/10.1016/j.jamda.2019.04.015
20. Johansen KL, Delgado C, Kaysen GA, et al. Frailty among patients receiving hemodialysis: evolution of components and associations with mortality. *J Gerontol A Biol Sci Med Sci*. 2019;74:380–386. https://doi.org/10.1093/gerona/gly206
21. Garcia-Canton C, Rodenas A, Lopez-Aperador C, et al. Frailty in hemodialysis and prediction of poor short-term outcome: mortality, hospitalization and visits to hospital emergency services. *Ren Fail*. 2019;41:567–575. https://doi.org/10.1080/0886022X.2019.1628061
22. Li Y, Zhang D, Ma Q, Diao Z, Liu S, Shi X. The impact of frailty on prognosis in elderly hemodialysis patients: A prospective cohort study. *Clin Interv Aging*. 2021;16:1659–1667. https://doi.org/10.2147/CIA.S329665
23. McAdams-DeMarco MA, Law A, Salter ML, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc*. 2013;61:896–901. https://doi.org/10.1111/jgs.12266
24. Vinson AJ, Bartolacci J, Goldstein J, Swain J, Clark D, Tennankore KK. Predictors of need for first and recurrent emergency medical service transport to emergency department after dialysis initiation. *Prehosp Emerg Care*. 2020;24:822–830. https://doi.org/10.1080/10903127.2019.1701157
25. Nixon AC, Brown J, Brotherton A, et al. Implementation of a frailty screening programme and Geriatric Assessment Service in a nephrology centre: a quality improvement project. *J Nephrol*. 2021;34:1215–1224. https://doi.org/10.1007/s40620-020-00878-y
26. Sun CY, Chao CT, Wu SH, et al. Effect of frail phenotype on cardiorenal risk and healthcare utilization in older patients with chronic kidney disease. *Cardiorenal Med*. 2024;14:1–23. https://doi.org/10.1159/000541807
27. Kennard A, Richardson A, Rainsford S, et al. Longitudinal frailty assessment in the prediction of survival among patients with advanced chronic kidney disease: a prospective observational single-centre cohort study. *BMJ Open*. 2024;14:e087189. https://doi.org/10.1136/bmjopen-2024-087189
28. Brown MA, Collett GK, Josland EA, Foote C, Li Q, Brennan FP. CKD in elderly patients managed without dialysis: survival, symptoms, and quality of life. *Clin J Am Soc Nephrol*. 2015;10:260–268. https://doi.org/10.2215/CJN.03330414
29. Foote C, Ninomiya T, Gallagher M, et al. Survival of elderly dialysis patients is predicted by both patient and practice characteristics. *Nephrol Dial Transplant*. 2012;27:3581–3587. https://doi.org/10.1093/ndt/gfs096
30. Kennard AL, Rainsford S, Glasgow NJ, Talaulikar GS. Use of frailty assessment instruments in nephrology populations: a scoping review. *BMC Geriatr*. 2023;23:449. https://doi.org/10.1186/s12877-023-04101-y
31. Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and chronic kidney disease: A systematic review. *Arch Gerontol Geriatr*. 2017;68:135–142. https://doi.org/10.1016/j.archger.2016.10.007
32. *Palliative care Outcome Scale (POS) - IPOS-Renal and Translations*. Copywrite Cicely Saunders Institute. 2012. 2012. Accessed October 3, 2019. https://pos-pal.org/maix/ipos-renal-in-english.php
33. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. *Prev Chronic Dis*. 2006;3:A118.
34. Johansen KL, Chertow GM, Jin C, Kutner NG. Significance of frailty among dialysis patients. *J Am Soc Nephrol*. 2007;18:2960–2967. https://doi.org/10.1681/ASN.2007020221

35. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383. https://doi.org/10.1016/0021-9681(87)90171-8

36. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173:676–682. https://doi.org/10.1093/aje/kwq433

37. Yadla M, John JP, Mummadi M. A study of clinical assessment of frailty in patients on maintenance hemodialysis supported by cashless government scheme. *Saudi J Kidney Dis Transplant*. 2017;28:15–22. https://doi.org/10.4103/1319-2442.198102

38. Delgado C, Shieh S, Grimes B, et al. Association of self-reported frailty with falls and fractures among patients new to dialysis. *Am J Nephrol*. 2015;42:134–140. https://doi.org/10.1159/000439000

39. Li J, Wang Z, Zhang Q, et al. Association between disability in activities of daily living and phase angle in hemodialysis patients. *BMC Nephrol*. 2023;24:350. https://doi.org/10.1186/s12882-023-03400-1

40. Subramaniam A, Ueno R, Tiruvoipati R, et al. Defining ICD-10 surrogate variables to estimate the modified frailty index: a Delphi-based approach. *BMC Geriatr*. 2022;22:422. https://doi.org/10.1186/s12877-022-03063-x

41. Lai HY, Huang ST, Chen LK, Hsiao FY. Development of frailty index using ICD-10 codes to predict mortality and rehospitalization of older adults: an update of the multimorbidity frailty index. *Arch Gerontol Geriatr*. 2022;100:104646. https://doi.org/10.1016/j.archger.2022.104646

42. Negative binomial regression: Stata data analysis examples. UCLA Advanced Research Computing Statistical Methods and Data Analytics. Accessed October 29, 2024. https://stats.oarc.ucla.edu/stata/dae/negative-binomial-regression

43. Hosmer Jr DW, Lemeshow S, Sturdivant RX. *Applied logistic regression*. 3rd ed. Wiley; 2013.

44. *StataCorp. Stata Statistical Software: release 17*. College Station, TX: StataCorp LLC; 2021.

45. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335:806–808. https://doi.org/10.1136/bmj.39335.541782.AD

46. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14:392–397. https://doi.org/10.1016/j.jamda.2013.03.022

47. Hurst H, Young HML, Nixon AC, Ormandy P, Brettle A, scoping review author collaborative for outcomes and care priorities for older people with ACKD. Outcomes and care priorities for older people living with frailty and advanced chronic kidney disease: a multi-professional scoping review. *Age Ageing*. 2022;51:afac296. https://doi.org/10.1093/ageing/afac296

48. Imamura K, Yamamoto S, Suzuki Y, et al. Comparison of the association between six different frailty scales and clinical events in patients on hemodialysis. *Nephrol Dial Transplant*. 2023;38:455–462. https://doi.org/10.1093/ndt/gfac047

49. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173:489–495. https://doi.org/10.1503/cmaj.050051

50. Worthen G, Vinson A, Cardinal H, et al. Prevalence of frailty in patients referred to the kidney transplant Waitlist. *Kidney360*. 2021;2:1287–1295. https://doi.org/10.34067/KID.0001892021

51. Floyd L, Byrne L, Morris AD, Nixon AC, Dhaygude A. The limitations of frailty assessment tools in ANCA-associated vasculitis. *J Frailty Aging*. 2023;12:139–142. https://doi.org/10.14283/jfa.2023.14

52. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62:722–727. https://doi.org/10.1093/gerona/62.7.722

53. Tonelli M, Wiebe N, Manns BJ, et al. Comparison of the complexity of patients seen by different medical subspecialists in a universal health care system. *JAMA Netw Open*. 2018;1:e184852. https://doi.org/10.1001/jamanetworkopen.2018.4852

54. Chattopadhyay T, Banerjee A, Mondal H. Causes of hospitalization in patients on maintenance hemodialysis with arteriovenous fistula in a Tertiary Care Hospital in West Bengal, India. *Saudi J Kidney Dis Transplant*. 2021;32:1418–1423. https://doi.org/10.4103/1319-2442.344762

55. Szeto CC, Chan GC, Ng JK, et al. Depression and physical frailty have additive effect on the nutritional status and clinical outcome of Chinese peritoneal dialysis. *Kidney Blood Press Res*. 2018;43:914–923. https://doi.org/10.1159/000490470

56. Ng JK-C, Kwan BC-H, Chow K-M, et al. Frailty in Chinese peritoneal dialysis patients: prevalence and prognostic significance. *Kidney Blood Press Res*. 2016;41:736–745. https://doi.org/10.1159/000450563

57. AIHW. Chronic Kidney Disease: Australian Facts. Accessed May 16, 2024. http://www.aihw.gov.au/reports/chronic-kidney-disease/chronic-kidney-disease

58. Sy J, Streja E, Grimes B, Johansen KL. The marginal cost of frailty among Medicare patients on hemodialysis. *Kidney Int Rep*. 2019;5:289–295. https://doi.org/10.1016/j.ekir.2019.11.020

59. Kutner NG, Zhang R, Huang Y, Herzog CA. Cardiac rehabilitation and survival of dialysis patients after coronary bypass. *J Am Soc Nephrol*. 2006;17:1175–1180. https://doi.org/10.1681/ASN.2005101027

60. Huang Y, Zhang R, Culler SD, Kutner NG. Costs and effectiveness of cardiac rehabilitation for dialysis patients following coronary bypass. *Kidney Int*. 2008;74:1079–1084. https://doi.org/10.1038/ki.2008.381

61. Forrest G, Nagao M, Iqbal A, Kakar R. Inpatient rehabilitation of patients requiring hemodialysis: improving efficiency of care. *Arch Phys Med Rehabil*. 2005;86:1949–1952. https://doi.org/10.1016/j.apmr.2005.04.006

62. Cowen TD, Huang CT, Lebow J, DeVivo MJ, Hawkins LN. Functional outcomes after inpatient rehabilitation of patients with end-stage renal disease. *Arch Phys Med Rehabil*. 1995;76:355–359. https://doi.org/10.1016/s0003-9993(95)80661-x

63. Morton RL, Webster AC, McGeechan K, et al. Conservative management and end-of-life care in an Australian cohort with ESRD. *Clin J Am Soc Nephrol*. 2016;11:2195–2203. https://doi.org/10.2215/CJN.11861115

64. Chen JC, Thorsteinsdottir B, Vaughan LE, et al. End of life, withdrawal, and palliative care utilization among patients receiving maintenance hemodialysis therapy. *Clin J Am Soc Nephrol*. 2018;13:1172–1179. https://doi.org/10.2215/CJN.00590118

65. ANZDATA 46th annual report 2023 (Data to 2022). Australia and New Zealand Dialysis and Transplant Registry. Accessed September 19, 2023. https://www.anzdata.org.au/report/anzdata-46th-annual-report-2023-data-to-2022/

66. Findlay MD, Donaldson K, Doyle A, et al. Factors influencing withdrawal from dialysis: a national registry study. *Nephrol Dial Transplant*. 2016;31:2041–2048. https://doi.org/10.1093/ndt/gfw074

67. Chen JHC, Brown MA, Jose M, et al. Temporal changes and risk factors for death from early withdrawal within 12 months of dialysis initiation-a cohort study. *Nephrol Dial Transplant*. 2022;37:760–769. https://doi.org/10.1093/ndt/gfab207

68. Chao CT, Wang J, Huang JW, Chan DC, Chien KL. Frailty predicts an increased risk of end-stage renal disease with risk competition by mortality among 165,461 diabetic kidney disease patients. *Aging Dis*. 2019;10:1270–1281. https://doi.org/10.14336/AD.2019.0216

69. Tonelli M, Wiebe N, Gill JS, et al. Frailty and clinical outcomes in patients treated with hemodialysis: A prospective cohort study. *Kidney Med*. 2023;5:100684. https://doi.org/10.1016/j.xkme.2023.100684

70. Kennard A, Rainsford S, Hamilton K, et al. Understanding the lived experience of frailty in the chronic kidney disease context using social cognitive theory: an exploratory qualitative study. *Int J Geriatr Gerontol*. 2024;8:180.

71. Isnard-Rouchon M, West M, Bennett PN. Exercise and physical activity for people receiving peritoneal dialysis: why not? *Semin Dial*. 2019;32:303–307. https://doi.org/10.1111/sdi.12784

72. Bennett PN, Bohm C, Harasemiw O, et al. Physical activity and exercise in peritoneal dialysis: International Society for Peritoneal Dialysis and the Global Renal Exercise Network practice recommendations. *Perit Dial Int*. 2022;42:8–24. https://doi.org/10.1177/08968608211055290

73. Cheng D, DuMontier C, Yildirim C, et al. Updating and validating the U.S. Veterans Affairs frailty index: transitioning from ICD-9 to ICD-10. *J Gerontol A Biol Sci Med Sci*. 2021;76:1318–1325. https://doi.org/10.1093/gerona/glab071

74. Gilbert T, Neuburger J, Kraindler J, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet*. 2018;391:1775–1782. https://doi.org/10.1016/S0140-6736(18)30668-8