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ORIGINAL ARTICLE

Frailty and comorbidity are independent predictors of outcome in patients referred for pre-dialysis education

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Abstract

Background: The incidence of chronic kidney disease (CKD) is rising and is likely to continue to do so for the foreseeable future, with the fastest growth seen among adults ≥75 years of age. Elderly patients with advanced CKD are likely to have a higher burden of comorbidity and frailty, both of which may influence their disease outcome. For these patients, treatment decisions can be complex, with the current lack of robust prognostic tools hindering the shared decision-making process. The current study aims to assess the impact of comorbidity and frailty on the outcomes of patients referred for pre-dialysis education.

Methods: We performed a single-centre study of patients ($n = 283$) referred for pre-dialysis education between 2010 and 2012. The Charlson Comorbidity Index (CCI) and Clinical Frailty Scale (CFS) were used to assess comorbid disease burden and frailty, respectively. Follow-up data were collected until February 2015.

Results: The CCI and CFS scores at the time of referral to the pre-dialysis service were independent predictors of mortality. Within the study follow-up period, 76% of patients with a high CFS score at the time of pre-dialysis education had died, with 63% of these patients not commencing dialysis before death.

Conclusion: A relatively simple frailty scale and comorbidity score could be used to predict survival and better inform the shared decision-making process for patients with advanced kidney disease.

Key words: chronic kidney disease, comorbidity, dialysis, frailty, outcomes

Introduction

Chronic kidney disease (CKD) is a common condition affecting ~1 in 10 of the UK population. The incidence of CKD is rising and is likely to continue to do so for the foreseeable future, driven mainly by the rise in type 2 diabetes and an ageing population [1, 2]. The highest incidence of end-stage renal disease (ESRD) now affects adults between the ages of 70 and 85 years at a rate three times higher than adults between the ages of 50 and 60 years, so that almost 25% of the dialysis population is at least 80 years old [3].

Elderly patients with advanced CKD are likely to have a higher burden of comorbidity and frailty that may influence their treatment choices and outcomes. Given the complex nature of the disease and treatment, a shared decision-making model is particularly important for these patients. Most renal units in the UK have now established a multidisciplinary pre-dialysis education programme to better support patients and their families. In our unit, a team of CKD nurse specialists was set up in 2004. A key part of the pre-dialysis workup includes a referral to a CKD nurse specialist who will then consult with the patient and invited

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family members at home. During this home visit, the nurse specialist provides education regarding kidney disease and modality choice, offers psychological and emotional support to pre-dialysis patients, explores potential treatment options and undertakes a physical and social assessment.

To better support the pre-dialysis education process, the last few years have witnessed renewed interest in developing risk prediction tools for patients with renal disease. Studies have demonstrated that readily available laboratory parameters may predict the progression of renal disease in patients with CKD [4]. Additionally, there have been an increasing number of studies assessing the impact of comorbidity and frailty on patient outcome [5–9].

There are numerous tools used in clinical practice to assess the degree of frailty. Recent studies in nephrology have assessed the Clinical Frailty Scale (CFS) as a predictor of outcome [10]. This relatively simple to use clinical tool describes nine categories ranging from very fit to terminally ill (Table 1). It has been demonstrated that frailty, as defined by the CFS, is an independent predictor of mortality in incident dialysis patients [11].

In spite of the growth of pre-dialysis education, few prognostic studies have focused on the survival of patients from the time of referral to the pre-dialysis service. Such studies may be useful since they would better inform the shared decision-making process by enabling the care team to provide patients and relatives with realistic, relevant outcomes linked to time of referral rather than outcomes that are linked to an estimated dialysis start date. This may be particularly relevant to patients with frailty or comorbidity, many of whom are more likely to die of comorbid disease than they are to enter a dialysis programme. One of the few studies to assess the pre-dialysis population demonstrated that comorbid disease burden was a predictor of outcomes from the time of dialysis decision-making; however, the study did not address the impact of frailty [12].

The aim of the current study was to assess the impact of both frailty and comorbidity on the outcome of patients referred to the pre-dialysis service.

Materials and methods

Patient population

The study was undertaken in a large tertiary referral renal unit with a catchment population of 1.4 million. According to unit policy, patients deemed at risk of progressing to ESRD are referred to a dedicated pre-dialysis team who undertake a home visit and provide pre-dialysis education. For each patient, baseline was defined as the time of the first pre-dialysis home visit. Baseline data were collected on 302 consecutive patients referred for pre-dialysis education between February 2010 and February 2012. Patients who were defined as late presenters (no prior contact with renal services in the 3 months prior to commencing dialysis) were excluded ($n = 19$). Follow-up data were collected until February 2015.

Data collection

Baseline clinical and laboratory data were collected from the renal unit's electronic database. The Charlson Comorbidity Index (CCI) was used to quantify comorbid disease burden at the time of pre-dialysis counselling [13]. The CCI uses a weighted scoring system based on the presence of comorbid diseases. The conditions and associated scores are shown in Table 2. Comorbidity data on each patient were obtained from clinic letters prior to the home visit. The presence or absence of each comorbid condition was verified with the patient at the time of the home visit. A detailed assessment of each patient's functional abilities and level of dependency was documented in the home visit report. The report is written according to a pre-specified template (Supplementary data, Table S1). The template includes sections on comorbidity, patient mobility, ability to cope with activities of daily living and the level of social support available or required. The reports contain all the information required to generate a CFS score for each patient [10].

At the end of the study follow-up period and prior to outcome analysis, pre-dialysis reports were reviewed by a single person (G.R.) who allocated a CFS score to each patient based on data contained in the report. For validity testing, reports were subsequently reviewed and scored by a second person (J.P.). When allocated CFS categories did not match (3% of cases), notes were reviewed and a final score agreed upon. For subgroup analysis, the frailty scores were subdivided into three categories according to functional ability—CFS scores 1–3 (managing well), CFS scores 4–5 (vulnerable to mildly frail), CFS scores 6–8 (moderate to severe frailty). The patient cohort did not include any patients with a CFS score of 9. The CCI scores were similarly subdivided into three subgroups (0–2, 3–4, >5).

Table 1. Clinical Frailty Scale (adapted from Rockwood *et al.* [10])

Score	Description
1	Very fit—People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.
2	Well—People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, e.g. seasonally.
3	Managing well—People whose medical problems are well controlled, but who are not regularly active beyond routine walking.
4	Vulnerable—While not dependent on others for daily help, often symptoms limit activities. A common complaint is being 'slowed up', and/or being tired during the day.
5	Mildly frail—These people often have more evident slowing and need help in high-order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
6	Moderately frail—People who need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
7	Severely frail—Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
8	Very severely frail—Completely dependent, approaching the end of life. Typically, they could not recover from even a minor illness.
9	Terminally ill—Approaching the end of life. This category applies to people with a life expectancy <6 months who are not otherwise evidently frail.

IADL, instrumental activities of daily living.

Table 2. Charlson Comorbidity Index

1 point	2 points	3 points	6 points
Myocardial infarction	Hemiplegia	Moderate or severe liver disease	Metastatic solid tumour
Congestive cardiac failure	Moderate or severe renal disease (serum creatinine >265 μmol/L)		AIDS
Peripheral vascular disease	Diabetes mellitus with organ damage		
Chronic pulmonary disease	Tumour without metastasis (exclude if >5 years from diagnosis)		
Diabetes mellitus (without end organ damage)	Lymphoma		
Cerebrovascular disease	Leukaemia		
Dementia			
Peptic ulcer disease			
Connective tissue disease			
Mild liver disease (without portal hypertension, includes chronic hepatitis)			

AIDS, Acquired immune deficiency syndrome.

Table 3. Patient demographic data

Age, median (IQR)	74 (63–81)
% Male	56
Serum albumin (g/L), mean (SD)	34 (6.2)
eGFR (mL/min) at time of visit, median (IQR)	16 (13–19)
Decline in eGFR (mL/min) in 6 months pre-visit, median (IQR)	3 (1–5)
Primary renal diagnosis	Diabetic nephropathy (18%) Ischaemic nephropathy (12%) Obstructive nephropathy (4%) Glomerulonephritis (6%) APKD (6%) Reflux (2%) Other (15%) Unknown (37%)
Follow-up time (months) prior to home visit, median (IQR)	24 (6–48)
Haemoglobin (g/L), mean (SD)	114 (15.6)
Patients on EPO (%)	30
BMI ($n = 149$), median (IQR)	28.8 (23.5–32.3)
PTH pmol/L, median (IQR)	22 (12–33)
Calcium (mmol/L), median (IQR)	2.38 (2.22–2.44)
Phosphate (mmol/L), median (IQR)	1.35 (1.16–1.53)
Ethnic group	
White European	94%
Asian (India/Pakistan)	5%
Chinese	0.5%
African/Caribbean	0.5%

APKD, Adult polycystic kidney disease; BMI, Body mass index; eGFR, Estimated glomerular filtration rate; EPO, Erythropoietin; IQR, inter quartile range; PTH, Parathyroid Hormone; SD, standard deviation.

Outcome

The primary outcome was 3-year mortality after the home visit. A secondary outcome was death prior to initiating dialysis (with patients censored at time of dialysis initiation).

Statistical analysis

Statistical analysis was done using SPSS (version 22). Where data were normally distributed, the mean and standard deviation are shown. For skewed data, the median and interquartile range (IQR) were used. Kaplan–Meier and log-rank test analyses were used to compare survival between groups. Cox proportional hazard regression models were used to assess the impact of individual parameters on patient survival. Only variables significant ($P < 0.05$) after univariate analysis were included in the final model. Log-minus-log plots were used to check the assumption of proportional hazards.

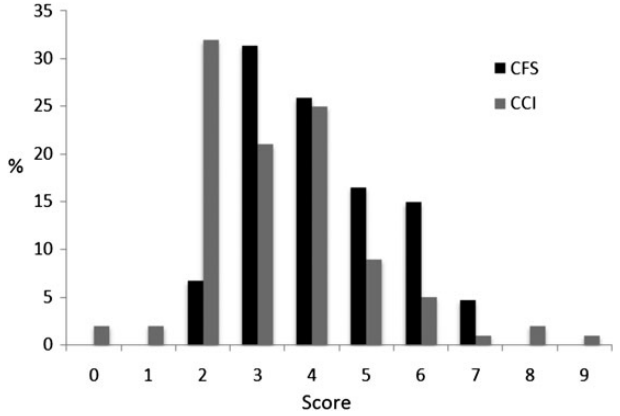

Fig. 1. Frequency distribution of Clinical Frailty Scale (CFS) and Charlson Comorbidity Index (CCI) scores.

Results

Patient demographics

Patient demographics are shown in Table 3. The median age of patients referred was 70 years with a median estimated glomerular filtration rate (eGFR) at the time of the home visit of 16 mL/min. The most common primary diagnosis was diabetic nephropathy.

Comorbidity and frailty

The distribution of CCI and CFS scores is shown in Figure 1. The majority of patients had at least mild frailty, with no patients fulfilling the 'very fit' category.

Modality choice

Table 4 presents the preferred modality choice of all patients (at the home visit) as well as the subsequent initial treatment modality (in those patients who progressed to ESRD). Of note, 18

Table 4. Modality choice made at home visit versus actual start modality

Preferred modality choice at home visit ($n = 283$)	Subsequent initial RRT modality in those progressing to ESRD ($n = 139$)
Unit HD (98)	Unit HD (56)
PD (72)	PD (30)
	Unit HD (18)
	Transplant (1)
Home HD (6)	Unit HD (3)
	Home HD (3)
Maximum conservative management (35)	Unit HD (1)
Transplant (3)	Transplant (2)
	PD (1)
Undecided (69)	Unit HD (17)
	PD (7)

HD, Haemodialysis; PD, peritoneal dialysis.

Table 5. Cox regression analysis of patient survival (only the significant variables after univariable analysis included in the final model)

	B	P-value	Exp (*B*)	95% CI for Exp (*B*)
Age (per year)	0.039	<0.001	1.04	1.021–1.059
CFS (per unit increase)	0.300	<0.001	1.35	1.161–1.570
CCI (per unit increase)	0.172	0.005	1.18	1.054–1.339
eGFR at time of home visit (per 1 mL/min)	−0.068	0.022	0.93	0.895–0.976

patients who initially opted for peritoneal dialysis (PD) started renal replacement therapy (RRT) on unit-based haemodialysis (HD). Patients with higher levels of frailty were more likely to choose conservative care (Supplementary data, Figure S1).

Survival analysis

There were 117 deaths within the 3-year follow-up period. The median survival among those patients who died was 560 days (range 5–1057). Based on presumed clinical importance, an a priori decision was made to assess the impact of age, serum albumin, eGFR, CFS score, CCI score, primary diagnosis, rate of eGFR decline and gender on survival. Initial univariate Cox regression analysis identified age, albumin, eGFR, CFS score and CCI score as statistically significant predictors of outcome. These variables were subsequently fitted into a multivariate Cox regression model to estimate the independent effect of each variable on survival. On multivariate analysis adjusted for age, gender and eGFR, the CFS and CCI scores remained independent predictors of mortality (Table 5).

Subgroup analysis was subsequently undertaken based on CFS and CCI scores. Patient demographics according to CFS subcategory are presented in Table 6. Survival according to subcategory is shown in Figure 2. There was a statistically significant difference between the groups, with the increasingly frail or comorbid subgroups having the worst survival. The percentage of patients dying within 3 years of the home visit increased with each increase in CFS score (Supplementary data, Figure S2). Given that RRT modifies an advanced CKD patient's trajectory, further survival analysis was done with patients censored at the time of RRT initiation. As shown in Figure 3, when censored for RRT, survival was worse for frailer, more comorbid subgroups.

A further analysis was done to assess patient outcomes 3-years after the home visit (Table 7). Of particular note, 63% of

Table 6. Patient demographics according to CFS category

CFS score	1–3 ($n = 101$)	4–5 ($n = 131$)	6–8 ($n = 51$)
Age (years), median (IQR)	64 (55–70)	72 (13)	75 (11)
% Male	58	52	60
Albumin (g/L), mean (SD)	35 (6.2)	35 (6.8)	33 (5.3)
eGFR (mL/min) at time of visit, median (IQR)	17 (14–19)	17 (6)	15 (6.5)
Decline in eGFR (mL/min) in 6 months pre-visit, median (IQR)	3 (1–6)	2 (3)	4 (4)
Primary diagnosis	Diabetic nephropathy (15%) Ischaemic nephropathy (6%) Obstructive nephropathy (5%) Glomerulonephritis (6%) APKD (15%) Reflux (4%) Other (16%) Unknown (33%)	Diabetic nephropathy (18%) Ischaemic nephropathy (16%) Obstructive nephropathy (4%) Glomerulonephritis (3%) APKD (2%) Reflux (2%) Other (25%) Unknown (30%)	Diabetic nephropathy (25%) Ischaemic nephropathy (16%) Obstructive uropathy (4%) Other (10%) Unknown (45%)
Follow-up time (months) prior to home visit, median (IQR)	23 (6–47)	24 (42)	26 (42)
Haemoglobin (g/L) at time of home visit, mean (SD)	114 (23)	109 (20)	117 (27)
Patients on EPO (%)	21	23	39
Parathyroid hormone (pmol/L) at time of home visit, median (IQR)	20 (10–33)	18 (17)	20 (12)
Serum calcium (mmol/L) at time of home visit, median (IQR)	2.4 (2.32–2.56)	2.3 (0.2)	2.3 (0.21)
Serum phosphate (mmol/L) at time of home visit, median (IQR)	1.35 (1.20–1.54)	1.3 (0.3)	1.4 (0.5)

patients with the highest frailty scores had died within 3 years of the pre-dialysis home visit without ever receiving RRT. The mean eGFR at the time of death in the cohort that died without dialysis was 15 mL/min, with 87% of patients dying with an eGFR >8 mL/min (the mean eGFR of patients commencing dialysis in our unit).

Discussion

In this study of CKD patients referred for pre-dialysis counselling, we found that CCI and CFS scores are independent predictors of mortality in patients referred to the pre-dialysis service. The development of prognostic tools incorporating such measures is likely to become increasingly important as the number of elderly patients developing advanced kidney disease continues to grow. Unlike the current study, many previous prognostic studies in CKD have focused on laboratory parameters or clinical diagnosis rather than on functional characteristics such as frailty [14, 15]. This may reflect the lack of robust and simple-to-use tools that evaluate a patient's performance status.

The last few years have witnessed renewed interest in the role of frailty as a prognostic marker [16]. Frailty is a common syndrome in elderly adults, described as a state of increased vulnerability to poor resolution of homeostasis after a stressor event [17]. Frailty increases the risk of adverse events, including falls, disability and death. Our study is the first to show that increasing frailty (as judged by the CFS score) also predicts mortality in patients referred to the pre-dialysis service.

Most renal units in the UK have now established a multidisciplinary pre-dialysis programme to better support patients and their families. The growth of these multidisciplinary

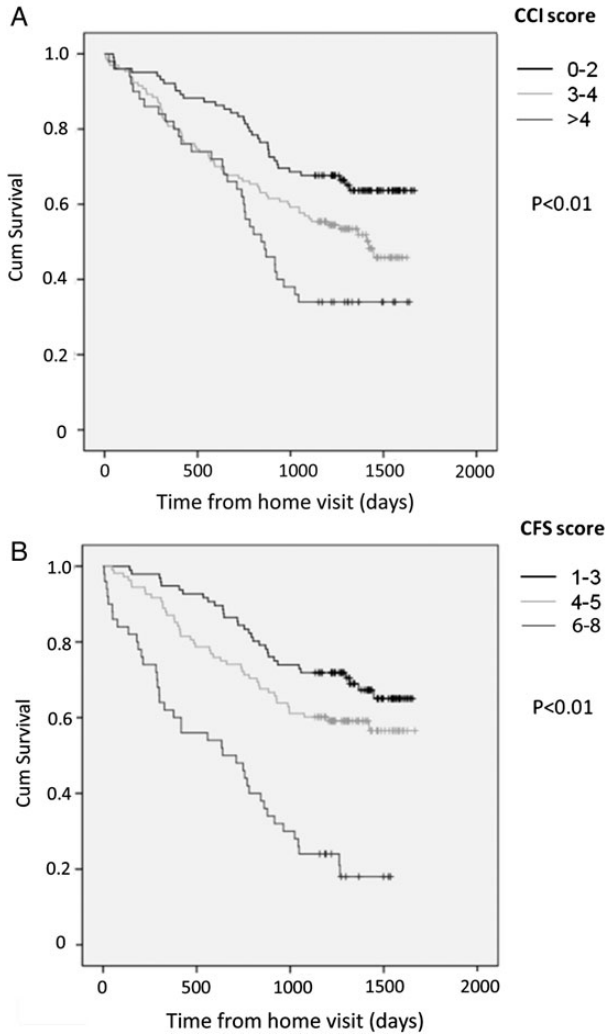

Fig. 2. Kaplan–Meier survival curves for (A) comorbidity and (B) frailty subgroups.

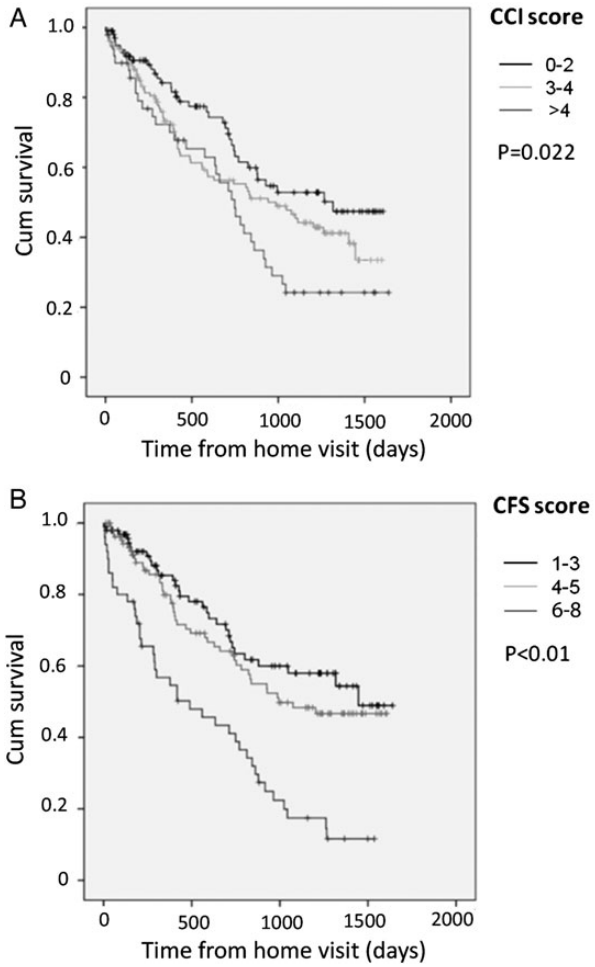

Fig. 3. Kaplan–Meier survival curves for (A) comorbidity and (B) frailty subgroups, censored at time of dialysis initiation.

Table 7. Patient outcomes 3-years after the home visit according to CFS category

	Died	Died (no RRT before death)	Alive (not commenced RRT)	Alive (with ongoing RRT)
CFS score 1–3 ($n = 101$)	28%	9%	27%	45%
CFS score 4–5 ($n = 131$)	39%	31%	31%	30%
CFS score 6–8 ($n = 51$)	76%	63%	16%	8%

programmes has been universally welcomed; however, it is increasingly clear that they must be underpinned by robust outcome data to guide patients and caregivers through what are often complex decisions. Incorporating a measure of frailty into the current pre-dialysis education programme could improve the shared decision-making process by providing patients and relatives with relevant and timely prognostic data. There is a pressing need to develop tools that better inform patients entering dialysis programmes about their prognosis. This is evidenced by studies demonstrating that patients often enter dialysis programmes unaware that ESRD confers such a poor prognosis, with patients dramatically overestimating even their 2-year survival rates [18].

As well as informing patients of their prognosis in the pre-dialysis setting, our study suggests that the CFS and CCI could also be used to better identify which patients should be referred for dialysis counselling. Of note, 76% of patients with a high CFS score at the time of pre-dialysis counselling had died within the study follow-up period, with 63% of these patients not commencing a dialysis programme before death. The majority of these patients had preserved eGFR at the time of death (>10 mL/min), suggesting that they did not die as a direct result of kidney failure. For these patients, discussions about dialysis may serve to increase anxiety with little tangible benefit. Routine use of CFS and comorbidity data may enable better identification of these patients in the CKD clinic and prevent unnecessary referral to the pre-dialysis service.

Our study has a number of limitations, including the relatively small population studied and the fact that it was a retrospective analysis of prospectively collected data. It is also not clear whether the creatinine-based eGFR calculation is valid in the face of frailty (and presumed weight loss, low muscle mass). The overall frailty score was high, which may reflect the fact that the median age of patients commencing dialysis in our unit was high (median age 68.7 years versus UK average age 66.5 [19]); additionally, our unit covers a catchment area that includes some of the most socially deprived regions in the UK [20]. Another limitation of our study is that the population studied was predominantly white European, so the results may not be applicable in regions containing a more diverse ethnic population.

We would suggest that future studies include a larger number of patients from multiple centres and that data on frailty be collected prospectively at the time of dialysis decision-making.

Conclusion

In conclusion, our data suggest that a relatively simple frailty scale and comorbidity score could be used to predict survival and better inform the shared decision-making process for patients with advanced kidney disease.

Supplementary data

Supplementary data are available online at http://ckj.oxfordjournals.org.

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Conflict of interest statement

None declared.

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