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Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease

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Abstract

Background. Novel strategies are required to efficiently manage the increasing number of patients diagnosed with chronic kidney disease (CKD). We sought to identify factors predicting outcome in patients with stage 4 CKD and to determine whether low-risk patients could be managed in primary care.

Methods. We performed a two-centre, retrospective cohort study including 396 patients with stage 4 CKD referred to nephrology clinics from 1998 to 2002. We utilized electronic databases to determine the incidence of renal replacement therapy (RRT) and mortality and the rate of deterioration in estimated glomerular filtration rate (eGFR) to the year end 2005.

Results. This was an elderly cohort, with 71.7% of patients aged ≥65 years. The risk of surviving to require dialysis fell with increasing age (HR 0.44; 95% CI: 0.23–0.84 for those >74 years verses those <65 years), in part due to the slower rate of decline in renal function in older patients (median fall in eGFR was −2.25, −1.38 and −0.86 ml/

min/1.73 m^2/year in those aged <65 years, 65–74 years and >74 years, respectively, $P < 0.0001$). Additional independent risk factors predicting RRT included: high baseline proteinuria (HR 6.26; 95% CI: 2.74–14.23 for >3 g/24 h versus <0.3 g/24 h), greater early decline in renal function (HR 3.86; 95% CI: 2.34–6.38 for ≥4 ml/min/1.73 m^2/year versus <4 ml/min/1.73 m^2/year), low baseline eGFR (HR 2.92; 95% CI: 1.61–5.30 for 15–19 versus 25–29 ml/min/1.73 m^2) and low haemoglobin (HR 3.16; 95% CI: 1.64–6.08 for <10 versus >12 g/dl). The 98 (24.7%) patients discharged to primary care had more stable renal function than those remaining under nephrology care (median change in eGFR of +0.20 versus −1.88 ml/min/1.73 m^2/year, $P = 0.0001$).

Conclusions. Most patients with stage 4 CKD, in particular the elderly, die without commencing RRT. Patients at low risk of progression can be identified and discharged safely to primary care with an active management plan.

Keywords: chronic kidney disease; elderly; progression; proteinuria; renal replacement therapy

Introduction

It is now recognized that chronic kidney disease (CKD) is a relatively common condition with ∼8% and 0.35% of the population falling into CKD stages 3 and 4, respectively [1–3]. Until recently, a significant proportion of CKD remained unrecognized, due to the low sensitivity of serum creatinine in detecting declining renal function, particularly in females and elderly patients [4,5]. The introduction of estimated glomerular filtration rate (eGFR) reporting, together with the requirement for UK general practitioners to maintain databases of patients with stages 3–5 of CKD [6], is likely to increase the rate of recognition of CKD and facilitate targeting of therapeutic interventions.

The very high prevalence of CKD in the elderly [1,3,7,8], as diagnosed according to the KDOQI [9] and UK guidelines [10], has prompted debate within the nephrology community as to whether the reduced eGFR in this population simply reflects a physiological ageing process rather than an intrinsic renal disease [11–14]. Indeed a diagnosis of CKD based on the percentile distribution of eGFR according to age and sex has been proposed [14]. Recent population-based studies have shown that age is an important predictor of the subsequent requirement for renal replacement therapy (RRT) [15–17], implying that a diagnosis of CKD has a different prognostic significance in elderly compared with younger persons. However it is recognized that there is a need for additional studies in this area, in particular an assessment of the ability of additional factors such as proteinuria to identify elderly patients who are at the greatest risk of progressive renal failure [13,14].

The increasing number of patients diagnosed with CKD has significant resource implications for nephrologists and for primary care. Current UK guidelines recommend that all patients with stage 4 CKD be at least discussed with a nephrologist [10]; however, it may be impractical and indeed unnecessary to provide ongoing nephrology follow-up for all of these patients. It is therefore critical that risk stratification algorithms are developed that permit us to identify those most at risk of progressive renal failure in order to prioritise these patients for intensive nephrology input.

In order to determine factors that predicted adverse outcomes in patients with advanced renal failure, we retrospectively identified all patients with stage 4 CKD who had been referred to two nephrology services and followed these patients to determine the subsequent incidence of death or RRT. In order to determine the effect of age we stratified baseline parameters and outcomes according to age group. Additionally, we sought to assess whether a subset of patients with stage 4 CKD could be safely managed in primary care by evaluating the outcome of patients at a low risk of progression who had been discharged from nephrology follow-up.

Subjects and methods

We employed our electronic databases to identify all patients with stage 4 CKD (eGFR ≥15 and <30 ml/min/1.73 m^2) referred to nephrology services of the Southern Health Board in Northern Ireland and the Lothian and Borders Health Boards in South-East Scotland (catchment areas of ∼310 000 and 900 000 persons, respectively) between 1 January 1998 and 31 December 2002 inclusive. In order to exclude those with acute renal failure, a minimum of two eGFR readings in the range 15–29 ml/min/1.73 m^2 and taken at least 3 months apart were required for each patient. As different methodologies were employed to measure serum creatinine between laboratories and within laboratories over time, the laboratory creatinine results were converted to isotope dilution mass spectrometry (ID-MS) traceable eGFR values according to the UK National External Quality Assessment Service (NEQAS) equation: $eGFR = 175 \times [0.011312 \times (SCr - c)/m]^{-1.154} \times age^{-0.203}$ (× 0.742 if female), where c and m are correction factors required to correct individual laboratory results to ID-MS values as determined by NEQAS [18,19]. Both of these regions have very small ethnic minority populations (<1% in Northern Ireland and ∼2.5% in South of Scotland); therefore, all patients were assumed to be Caucasian and no correction factor for ethnicity was included in the conversion [20,21].

Baseline characteristics included systolic and diastolic blood pressure as recorded at the first clinic attendance; 24 h proteinuria (g/24 h) measured by either urinary collection or by estimation from the protein (mg):creatinine (mmol) ratio in spot urine samples using the correction factor 0.0088 [22]. Renal diagnosis was as determined by the nephrologist responsible for the patient's care: renovascular disease was most often a clinical diagnosis and imaging of the renal vessels was uncommon; diabetic and hypertensive nephropathy were most often clinical and not histological diagnoses; glomerulonephritis and vasculitis were invariably histological diagnoses.

Patients were followed-up using computerized renal unit and patient administration system databases and by recourse to GP records where required. The rate of decline in eGFR was determined by subtracting the latest available laboratory eGFR result from that obtained at the first clinic attendance and dividing it by the time between readings. At least 6 months must have elapsed between the first and last readings in order to minimize the effect of fluctuations in eGFR. The early rate of decline in renal function was determined in a similar manner as above using the eGFRs from the initial clinic visit and from the first clinic attendance beyond 6 months from the baseline visit. Based on the early rate of change in renal function, patients were grouped into progressors (decline in eGFR ≥4 ml/min/1.73 m^2/year) and non-progressors (fall in eGFR <4 ml/min/1.73 m^2/year) as defined by the UK CKD Guidelines [10].

Statistical analysis was performed using the Stata software package, version 8.2 (StataCorp LP, TX, USA). Nephrology referral rates were calculated per 100 000 population based on the 2001 age-stratified population statistics for the respective catchment areas [20,21]. Subgroups were compared using the χ^2-test for categorical values and for continuous variables Student's t-test (ANOVA for multiple groups) and Mann–Whitney U-test (Kruskal–Wallis test for multiple groups) were employed for parametric and non-parametric distributions, respectively. Probabilities of death and of requiring RRT were calculated using separate Cox proportional

Table 1. Baseline characteristics of the cohort by age group

	<65 (% total)	65–74 (% total)	≥75 (% total)	Combined cohort (% total)
Total	112 (28.3)	150 (37.9)	134 (33.8)	396 (100.0)
South East of Scotland	70 (17.7)	95 (24.0)	76 (19.2)	241 (60.9)
Northern Ireland	42 (10.6)	55 (13.9)	58 (14.7)	155 (39.1)
Sex				
Female	50 (12.6)	69 (17.4)	77 (19.4)	196 (49.5)
Male	62 (15.7)	81 (20.5)	57 (14.4)	200 (50.5)
Aetiology of CKD[a]				
Renovascular/hypertension	20 (5.1)	70 (17.7)	64 (16.2)	154 (38.9)
Diabetic Nephropathy	29 (7.3)	21 (5.3)	11 (2.8)	61 (15.4)
Glomerulonephritis/vasculitis	12 (3.0)	6 (1.5)	2 (0.5)	20 (5.1)
Other/ unknown	51 (12.9)	53 (13.4)	57 (14.4)	161 (40.7)
Creatinine (μmol/l)[a]	229 (205–275)	220 (189–262)	210 (180–244)	220 (189–263)
eGFR (ml/min/1.73 m^2)				
<20	30 (7.6)	44 (11.1)	45 (11.4)	119 (30.1)
20–24	45 (11.4)	58 (14.7)	49 (12.4)	152 (38.4)
≥25	37 (9.3)	48 (12.1)	40 (10.1)	125 (31.6)
Systolic BP (mmHg)[a]	148.3 (±25.0)	157.1 (±27.0)	155.2 (±26.1)	154.0 (±26.3)
Diastolic BP (mmHg)[a]	82.7 (±13.6)	81.3 (±12.9)	78.6 (±13.0)	81.0 (±13.2)
Proteinuria (g/24 h)[a]				
<0.3	26 (7.1)	53 (14.4)	60 (16.4)	139 (37.9)
0.3–0.99	25 (6.8)	36 (9.8)	27 (7.4)	88 (24.0)
1–2.99	36 (9.8)	43 (11.7)	19 (5.2)	98 (26.7)
≥3	19 (5.2)	12 (3.3)	11 (3.0)	42 (11.4)
Haemoglobin (g/dl)				
<10	13 (3.4)	26 (6.7)	27 (7.0)	66 (17.1)
10–11.99	52 (13.4)	62 (16.0)	56 (15.5)	170 (43.9)
≥12	46 (11.9)	56 (14.5)	49 (12.7)	151 (13.2)

Values are expressed as count (percentage), mean (±SD) or median (interquartile range).
[a]Variables that were significantly different ($P < 0.05$) between age groups.

hazard regression models, giving hazard ratios (HR with 95% CI). For each model, variables demonstrating an association with the outcome at $P < 0.10$ on univariate analysis were entered into a multivariate model. The least significant variable using the likelihood ratio (LR) test was removed sequentially until only variables with $P < 0.05$ remained. Cumulative hazard curves were generated for death and for RRT, adjusted for variables that remained significant in the Cox models. The assumptions underpinning the proportional hazards approach were checked using the time-dependent covariate method and plots of Schoenfeld residuals.

Results

We identified 396 patients with stage 4 CKD (mean baseline eGFR 22.5 ml/min/1.73 m^2) referred to the nephrology service from 1998 to 2002 inclusive. The baseline characteristics of the Northern Ireland and South-East of Scotland cohorts were similar; the only significant difference was a higher mean diastolic blood pressure in the Northern Ireland cohort (82.9 versus 79.9 mmHg in Scotland, $P = 0.04$, data not shown).

This was an elderly population (median age at referral of 71.6 years), with more than one-third of the cohort aged >75 years. The rate of referral increased dramatically with age up to 80 years, before declining in the very elderly (Figure 1). Older patients were significantly more likely to have a diagnosis of renovascular disease or hypertensive nephropathy (Table 1). Proteinuria lessened with increasing age at referral, while pulse pressure increased. While the median creatinine at referral was lower in older patients, there was no difference in the baseline eGFR among the age groups (mean eGFR 22.7, 22.5 and 22.3 ml/min/1.73 m^2 in those aged <65, 65–74 and ≥75 years, respectively, $P = 0.74$).

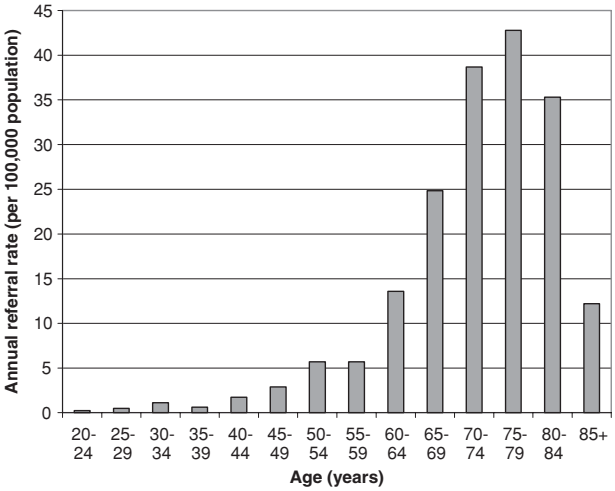

Fig. 1. Annual referral rate (per 100000 population) stratified by age group of stage 4 CKD to the outpatient nephrology clinics in the Southern Health Board, Northern Ireland and Lothian and Borders Health Boards, South-East Scotland.

The median follow-up period from first clinic attendance was 3.76 years, representing a total follow-up time of 1490

Table 2. Risk of death and of surviving to commence RRT

	Death			RRT		
	Unadjusted HR	Adjusted HR[a]	P[b]	Unadjusted HR	Adjusted HR[c]	P[b]
Region			–			
South of Scotland	1.0	–	–	1.0	–	–
Northern Ireland	0.85 (0.63–1.15)	–	–	0.72 (0.47–1.12)	–	
Age at referral (years)			0.0001			0.0290
<65	1.0	1.0		1.0	1.0	
65–74	1.89 (1.25–2.84)	1.83 (1.21–2.77)		0.68 (0.43–1.07)	0.85 (0.52–1.41)	
≥75	2.54 (1.69–3.82)	2.40 (1.59–3.62)		0.38 (0.21–0.70)	0.44 (0.23–0.84)	
Sex			–			–
Female	1.0	–	–	1.0	–	
Male	1.01 (0.75–1.35)	–	–	1.63 (1.06–2.50)		
Aetiology of CKD			–			0.0563
Renovascular/hypertension	1.0	–	–	1.0	1.0	
Diabetic nephropathy	0.84 (0.54–1.31)	–	–	1.61 (0.92–2.82)	0.52 (0.26–1.02)	
GN/vasculitis	0.26 (0.08–0.83)	–	–	2.46 (1.17–5.17)	1.53 (0.64–3.63)	
Other/unknown	0.87 (0.63–1.19)	–	–	0.82 (0.49–1.36)	0.80 (0.45–1.40)	
Early rate of decline in eGFR (ml/min/1.73 m^2/year)			0.0110			0.0003
<4	1.0	1.0		1.0	1.0	
≥4	1.46 (1.08–1.97)	1.51 (1.11–2.07)		4.42 (2.90–6.75)	3.86 (2.34–6.38)	
eGFR (ml/min/1.73 m^2)			0.0045			<0.0001
≥25	1.0	1.0		1.0	1.0	
20–24	1.41 (0.96–2.09)	1.23 (0.82–1.84)		1.51 (0.85–2.68)	1.13 (0.61–2.08)	
<20	2.04 (1.38–3.00)	1.88 (1.26–2.82)		3.22 (1.84–5.66)	2.92 (1.61–5.30)	
Diastolic BP (per 10 mmHg increase)	0.86 (0.77–0.96)	0.86 (0.77–0.96)	0.0092	1.24 (1.06–1.44)		–
Proteinuria (g/24 h)						0.0002
<0.3	1.0	–	–	1.0	1.0	
0.3 < 1	0.92 (0.60–1.34)	–	–	2.57 (1.28–5.12)	1.97 (0.96–4.06)	
1 < 3	1.12 (0.76–1.63)	–	–	3.51 (1.85–6.64)	2.36 (1.20–4.64)	
≥3	1.14 (0.68–1.91)	–	–	10.03 (5.14–19.56)	6.26 (2.74–14.23)	
Haemoglobin (g/dl)			0.0079			0.0022
≥12	1.0	1.0		1.0	1.0	
10 < 12	1.26 (0.89–1.78)	1.12 (0.79–1.60)		1.80 (1.11–2.91)	1.82 (1.10–3.02)	
<10	2.43 (1.63–3.63)	1.93 (1.27–2.93)		2.55 (1.38–4.71)	3.16 (1.64–6.08)	

[a]Adjusted HR for death are adjusted for age, baseline GFR, rate of GFR decline, baseline haemoglobin, baseline diastolic BP.
[b]P for likelihood ratio test.
[c]Adjusted HR for surviving to require RRT are adjusted for age, cause of chronic kidney disease, baseline GFR, rate of GFR decline, baseline haemoglobin, baseline proteinuria.

person years. In total 180 (45.4%) patients died, 89 (22.5%) of the cohort were treated with RRT and 10 (2.5%) patients were lost to follow-up. There were no significant differences in the rates of RRT or death between the Northern Ireland and South-East Scotland cohorts ($P = 0.16$ and $P = 0.27$, respectively). Crude survival at 1, 3 and 5 years was 89.6, 71.2 and 52.5%, while the percentage of patients who had commenced RRT was 3.8, 11.5 and 24.7%, respectively. A total of 20 (5.1%) patients opted for a conservative management strategy for their renal failure, 18 of whom subsequently died. There was no significant difference in the median age of those opting for a conservative rather than a dialytic management strategy for their renal failure (73.2 versus 71.3 years, $P = 0.34$).

In a multivariate analysis, the risk of being offered RRT and of death increased at lower levels of baseline eGFR and haemoglobin and if the early rate of decline in renal function was >4 ml/min/1.73 m^2/year (Table 2). Proteinuria was a strong predictor of RRT ($P = 0.0002$), but not of death.

As expected, the risk of death increased with age; conversely, however, the risk of surviving to be offered RRT fell, with hazard ratio 0.44 (95% CI: 0.23 to 0.84) for patients aged ≥75 years when compared to patients aged <65 years (Table 2). Indeed in patients ≥75 years the need for RRT within 3 years of referral was largely confined to those with a baseline eGFR<20 ml/min/1.73 m^2 or a renal diagnosis of glomerulonephritis/vasculitis (Table 3). The adjusted cumulative hazard curves for survival and RRT (Figure 2) demonstrate that the reduced incidence of RRT in the elderly subgroup is at least in part due to the fact that they are more likely to die prior to progression to RRT. However, the rate of progression of renal failure was also slower in older patients, with the median (IQR) rate of decline in renal function of −2.25 (−4.2 to −0.6) ml/min/1.73 m^2/year, −1.38 (−3.2 to +0.4) ml/min/1.73 m^2/year and −0.86 (−2.3 to +1.2) ml/min/1.73 m^2/year for those aged <65 years, 65–74 and ≥75 years, respectively ($P = 0.0001$). There did not appear to be a bias towards commencing RRT at a lower eGFR in older patients; the mean eGFR at the time of initiation of RRT was 8.0, 8.4 and 9.8 ml/min/1.73 m^2 in those aged <65 years, 65–74 and ≥75 years, respectively ($P = 0.07$). Furthermore, in the subgroup of patients who died without commencing RRT, there was no difference between the age groups in the mean eGFR at the last clinic visit before death (19.7, 21.6 and 20.7 ml/min/1.73 m^2 for those aged <65,

Table 3. Reference table showing cases per 100 referrals expected to survive to require RRT at 1, 3 and 5 years after referral, by age and eGFR at referral and cause of underlying CKD

		Age <65 years			Age 65–74 years			Age ≥75 years		
Aetiology of CKD	eGFR at referral (ml/min/1.73 m^2)	1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years
Renovascular/hypertension	<20	4.0	18.7	54.6	3.4	16.1	48.9	1.8	8.7	29.3
	20–24	1.6	7.7	26.3	1.3	6.6	22.8	6.9	3.5	12.5
	≥25	1.4	6.9	23.7	1.2	5.9	20.5	0.6	3.1	11.2
Diabetic nephropathy	<20	2.1	10.2	33.5	1.8	8.7	29.3	0.9	4.6	16.4
	20–24	0.8	4.1	14.6	0.7	3.5	12.5	0.4	1.8	6.7
	≥25	0.7	3.6	13.1	0.6	3.1	11.2	0.3	1.6	6.0
GN/vasculitis	<20	6.0	27.1	70.0	5.1	23.6	64.1	2.7	13.0	41.1
	20–24	2.4	11.5	37.2	2.0	9.9	32.3	1.1	5.2	18.5
	≥25	2.1	10.3	33.8	1.8	8.8	29.6	0.9	4.7	16.6
Other/unknown	<20	3.2	15.2	46.7	2.7	13.1	41.4	1.4	7.0	24.1
	20–24	1.2	6.2	21.6	1.1	5.3	18.6	0.6	2.8	10.1
	≥25	1.1	5.5	19.4	0.9	4.7	16.7	0.5	2.5	9.0

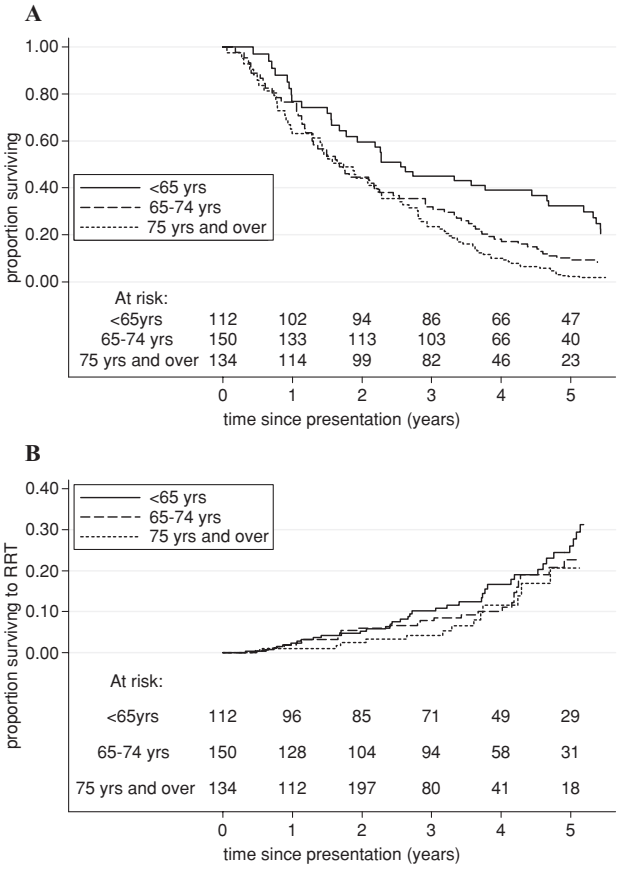

Fig. 2. (**A**) Proportion of patients surviving by age group at referral. Curves are generated from the Cox regression equation and are adjusted for baseline haemoglobin, eGFR and diastolic blood pressure and early rate of change in renal function. (**B**) Cumulative risk of likelihood of renal replacement therapy by age at referral. Curves are generated from the failure function of the Cox regression equation and are adjusted for early rate of change in eGFR and level of proteinuria, haemoglobin and eGFR at referral.

65–74 and ≥75 years, respectively, $P = 0.73$), suggesting that elderly patients were not dying of advanced renal failure.

A total of 98 (24.7%) patients were discharged from regular nephrology review to primary care with an active management plan. Patients who were discharged were more likely to be elderly and female and their renal diagnosis was more often ischaemic/hypertensive nephrosclerosis or unclassified. They had marginally greater baseline eGFR, higher haemoglobin, slower early deterioration in eGFR and low-grade proteinuria (Table 4). Following discharge they had more stable renal function (median (IQR) gain in eGFR of +0.20 (−1.3 to +1.1) ml/min/1.73 m^2/year) compared with those remaining under regular nephrology review (median (IQR) fall of −1.88 (−3.7 to +0.1) ml/min/1.73 m^2/year, $P < 0.0001$). The mortality rate was no different between the two groups. Only seven patients were re-referred to the nephrology services and none subsequently commenced RRT.

Discussion

This retrospective analysis of the progression and outcome of patients referred to the nephrology service with stage 4 CKD illustrates that, despite having advanced renal failure (mean baseline eGFR 22.5 ml/min/1.73 m^2), only approximately one-quarter of patients require RRT after 5 years of follow-up. This is in keeping with a previous study, which included 777 patients with stage 4 CKD and found that after 5 years of follow-up the mortality rate exceeded the rate of RRT (45.7% versus 19.9%, respectively) [23].

Age had a strong effect on the risk of subsequent RRT, with patients aged ≥75 years being 56% less likely to subsequently commence dialysis than those aged <65 years. A similar effect of age was observed in a recent study from the US Veterans Affairs Healthcare System which showed that in (almost exclusively male) patients with stage 4 CKD, those aged 65–74, 75–84 and ≥85 years had a reduction in risk of RRT of 64, 74 and 88%, respectively, compared to those aged 18–44 years [15]. An age-dependent reduction in the risk of RRT was also observed in two additional studies that included patients with moderate [16] and severe kidney disease [17], respectively.

Table 4. Characteristics of the patients according to whether or not they were discharged from ongoing nephrology care

	Discharged to primary care ($n = 98$)	Ongoing nephrology follow-up ($n = 263$)	*P*-value
Male (%)	37 (38.8)	145 (55.5)	0.003
Age (years)	75.5 (69.2–80.3)	69.8 (60.7–75.3)	<0.0001
Aetiology of CKD			
Renovascular/hypertension	44 (12.2)	98 (27.1)	0.0002
Diabetic nephropathy	4 (1.1)	56 (15.5)	
Glomerulonephritis/vasculitis	2 (0.6)	16 (4.4)	
Other/unknown	48 (13.3)	93 (25.8)	
Baseline eGFR (ml/min/m^2)	23.5 (±3.6)	22.1 (±4.0)	0.003
Early rate of change in eGFR (ml/min/1.73 m^2/year)	+1.75 (−2.0 to +7.1)	−2.1 (−6.1 to +2.5)	<0.0001
Systolic BP (mmHg)	151.0 (±24.7)	156.1 (±27.8)	0.12
Diastolic BP (mmHg)	79.0 (±11.1)	82.1 (±14.1)	0.05
Proteinuria (g/24 h)	0.19 (0.09–0.63)	0.8 (0.2–2.0)	<0.0001
Haemoglobin (g/dl)	12.0 (10.9–13.1)	11.3 (10.3–12.4)	0.004

Values are expressed as count (percentage of total), mean (±SD) or median (interquartile range).

Although the reduction in acceptance for RRT was partly due to the increase in the competing risk of death with age, in addition elderly patients had a slower rate of decline in renal function of ∼1 ml/min/1.73 m^2/year, comparable to the estimated physiological rate of age-related decline [24]. While the Veteran Affairs study also showed that older patients were at a lower risk of a rapid decline in renal function, we were additionally able to demonstrate that they exhibited low-grade proteinuria, indicating that it is likely that few of this age-group have an active intrinsic glomerular disease. However, only a minority of people develop advanced renal dysfunction with age; therefore, CKD in the elderly is still likely to represent a pathological process, most commonly renal hypoperfusion due to intra and extrarenal atherosclerosis, hypertension or impaired cardiac function, resulting in slowly progressive glomerulosclerosis [25,26]. Hence, in the elderly population CKD is often a marker of multiple co-morbidities and thus mortality, whereas in younger patients it is more likely to reflect the consequences of an intrinsic renal disease and hence the risk of subsequent RRT. This hypothesis is supported by data from the current study; only 18.6% of patients ≥75 years compared with 62.5% of patients <65 years were diagnosed with an intrinsic renal disease such as diabetic nephropathy, glomerulonephritis, obstructive nephropathy, interstitial nephritis or polycystic kidney disease. It is important, however, to recognize that while elderly patients with stage 4 CKD are relatively less likely to have an intrinsic renal disease than younger patients, the absolute incidence of primary renal disease remains greater in older patients.

Current UK guidelines advocate that all patients diagnosed with stage 4 CKD should be at least discussed with a nephrologist [10], with more recent updates stressing the importance of the rate of decline in eGFR in the timing of referral [27]. While there is good evidence that attendance at a nephrology clinic is associated with a reduction in the rate of decline in renal function [28], the benefit was largely restricted to those with progressive renal dysfunction prior to referral. The benefit of ongoing nephrology care for those with advanced, but stable chronic kidney disease is less clear.

We determined that it was possible to identify a subset (approximately one quarter) of mostly elderly patients with stage 4 CKD who were at low risk of progressive renal dysfunction and following discharge from nephrology care these patients had stable renal function in the community. Interestingly, the clinical characteristics of those discharged to primary care correlate closely with factors that predict a good renal prognosis in the multivariate analysis. Broadly similar selection criteria were employed in a previous study to enrol patients with stage 4 CKD to a shared care scheme (SCS) in which they were discharged from the nephrological follow-up but had their blood results checked in primary care and monitored remotely by nephrologists [29]. In our study, the stability of the renal function in the patients who were discharged suggests that remote nephrological input is not necessary, provided an agreed, individualized management plan is in place; however, a small proportion of patients (<10%) with deteriorating renal function or progressive anaemia will be subsequently be referred back to the nephrology service.

An alternative strategy would be to introduce 'virtual clinics' which could provide E-mail advice to primary care and prioritise patients for ongoing nephrology input by employing variables such as current eGFR, rate of decline in renal function, haemoglobin level and proteinuria. Our data demonstrate the potential of this approach: less than 1 in 10 patients aged ≥75 years commenced RRT after 5 years of follow-up providing they did not have either very advanced renal failure (baseline eGFR <20 ml/min/m^2) or moderate-to-severe proteinuria >1 g/24 h. Such clinics would reduce the need for elderly patients, who often have multiple co-morbidities [8], to attend hospital clinics and enable general practitioners to obtain timely advice on a much greater number of patients than could be seen in the traditional clinic setting.

It is however important to emphasize that all patients were seen at a nephrology clinic at least once and that during these visits measures such as aggressive treatment of hypertension may have been instituted that could have had a subsequent beneficial effect on the rate of decline in renal function. Unfortunately, we do not have accurate

medication records that would be informative in this regard. Hence, the outcomes observed in the current study cannot be directly extrapolated to patients in the community who have not received any nephrology input.

A major strength of our study is that there were virtually complete follow-up data (<3% missing) over a median follow-up period of almost 4 years. In addition, unlike many population-based studies, renal diagnoses and baseline blood pressure and proteinuria measurements were available for the great majority of patients, and hence, we were able to examine the effect of these variables on outcomes. It was a two-centre study and as the baseline patient characteristics and outcomes were similar between the centres, it is likely to be representative of the Caucasian population in the UK; however, different patterns may be encountered in regions with high ethnic minorities.

A weakness of the study is that it comprised patients attending nephrology clinics, thereby introducing referral bias. It has previously been demonstrated that elderly patients with CKD are much less likely to be referred to a nephrologist [5]. This was evident in our own population as, although the incidence of CKD increases exponentially with age [1–5], the referral rate fell in patients ≥80 years (Figure 1). As elderly patients are less likely to progress to RRT, our study is therefore likely to have overestimated the subsequent need for dialysis or transplantation.

In addition, we followed patients who were referred between 1998 and 2002, prior to the introduction of a number of measures that may affect the referral and treatment of patients with CKD such as eGFR reporting, inclusion of renal domains in the Quality Outcomes Framework initiative [6] and publication of UK guidelines for the management of CKD [10]. Hence, our historical cohort may not be entirely representative of the characteristics of those currently referred to the nephrology service; indeed, more recently we have observed that a greater proportion of those referred with stage 4 CKD have been elderly patients, who were not previously recognized to have advanced renal failure. Furthermore, more aggressive management of CKD in the community may have led to an improvement in patient survival and renal outcome compared with that observed in our historical cohort.

As we are employing retrospective observational data, we cannot exclude the possibility that the lower uptake of RRT in older patients is due to age-related bias in decision making regarding the timing or appropriateness of RRT. For instance, the slower rate of decline in renal function, the lack of a specific renal diagnosis or increased comorbidities may dissuade nephrologists from commencing RRT in elderly patients. However, several indicators point to the fact that this is not a significant factor in the reduction in the incidence of RRT in more elderly patients. First, elderly patients who died without commencing dialysis had a mean eGFR of 20 ml/min/1.73 m^2 at the time of their last clinic attendance, suggesting that they died of co-morbidities other than their renal failure. We cannot, however, rule out the possibility of a rapid deterioration in renal function immediately prior to death, and unfortunately, we do not have access to death certification, which may have indicated if renal failure was considered to contribute significantly to death. Secondly, we did not observe any significant difference between the mean eGFR at the initiation of RRT between those ≥75 years and <65 years, indicating that the eGFR threshold for commencing dialysis was not higher for older patients. Thirdly, there were similar proportions of patients aged <65 years and ≥75 years with a last recorded eGFR <10 ml/min/1.73 m^2 who were not receiving RRT, indicating that there was no systematic bias against the initiation of dialysis on the basis of advanced age alone. Finally, there was no significant difference in the median age of the patients opting for (73.2 years) or against (71.3 years) conservative care, implying that the reduced incidence of RRT in the elderly patients was not primarily due to a larger proportion of this age group opting for non-dialytic management of their renal failure.

In conclusion, the current study has identified that many elderly patients with stage 4 CKD have low-grade proteinuria and slowly declining renal function, and as their renal failure is more likely to reflect vascular co-morbidity than a primary renal disease, they are much more likely to die than progress to require RRT. As elderly patients comprise the bulk of those with stage 4 CKD, careful collaboration at the primary care/nephrology interface will be required to avoid unnecessary hospital visits for this group of patients, and future research should be directed towards developing efficient, patient-orientated strategies for managing this cohort of patients.

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(See related article by A. Levin. Predicting outcomes in CKD: the importance of perspectives, populations and practices. *Nephrol Dial Transplant* 2009; 24: 1724–1726.)

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Microbial inactivation properties of a new antimicrobial/antithrombotic catheter lock solution (citrate/methylene blue/parabens)

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Abstract

Background. Microbial infections are the most serious complications associated with indwelling central venous catheters. A catheter lock solution that is both antibacterial and antithrombotic is needed. The goal of this study was to determine whether a new catheter lock solution containing citrate, methylene blue and parabens has antimicrobial properties against planktonic bacteria and against sessile bacteria within a biofilm. These effects were compared to the antimicrobial properties of heparin at 2500 units/ml.

Methods. The tested solution (C/MB/P comprising 7% sodium citrate, 0.05% methylene blue and 0.165% parabens) and individual components were challenged against gram-positive and gram-negative organisms and fungi. Control solutions were heparin with preservatives. Studies included evaluation of eradication of planktonic bacteria and sessile organisms in a biofilm grown on polymeric and glass coupons. Biofilm samples were inspected by scanning electron microscopy, atomic force microscopy and vital stains.

Results. The C/MB/P solution, contrary to heparin, kills most tested planktonic microorganisms within 1 h of incubation. All tested organisms have an MIC of 25% or less of the original concentration of a new catheter lock.