



ORIGINAL ARTICLE

Patterns of progression of chronic kidney disease at later stages

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Abstract

Background: At later stages of chronic kidney disease (CKD), a pattern of linear and irreversible renal function decline is thought to be the most common. The objective of this study was to describe the characteristics of the different patterns of CKD progression, and to investigate potentially modifiable factors associated with the rate of decline of renal function.

Methods: This was a retrospective, observational study in a cohort of adult patients with CKD Stage 4 or 5 not on dialysis. Decline in renal function was estimated as the slope of the individual linear regression line of estimated glomerular filtration rate (eGFR) over time. The following patterns of CKD progression were considered: unidentifiable, linear, nonlinear (curvilinear) and positive (improvement of renal function).

Results: The study group consisted of 915 patients (mean \pm SD age 65 ± 14 years, 48% females, median follow-up time 16 months). A linear pattern was observed in 38%, unidentifiable in 23%, nonlinear in 24% and positive in 15% of the study patients. The mean eGFR slope was: -3.35 ± 4.45 mL/min/year. Linear and unidentifiable patterns were associated with more rapid loss of renal function. By multiple linear and logistic regression analysis, the magnitude of proteinuria, the systolic blood pressure and the treatment with dual renin–angiotensin system blockade were associated with more rapid CKD progression. On the contrary, older age and discontinuation of commonly prescribed medication with potential influence on renal function or eGFR measurements were associated with slower CKD progression.

Conclusions: A majority of patients with advanced CKD show patterns of renal function decline different from linear, and several of the main determinants of CKD progression are potentially modifiable.

Key words: chronic kidney disease, dual blockade renin–angiotensin system, patterns of CKD progression, proteinuria

Introduction

Until recent years, it was thought that chronic kidney disease (CKD) exhibited a predominantly linear progression pattern [1–3], with a more rapid decline of renal function at later stages [4–6]. Thus, it seemed difficult to slow or halt the progression of CKD at Stage 4 or 5.

However, recent observational studies have shown that patterns of CKD progression may be highly heterogeneous, and trajectories of glomerular filtration rate (GFR) over time can fit patterns different from linear [7–13]. Knowledge of the

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determinants of these different CKD progression patterns may be of great interest for the management of this disease.

The aims of this observational study in a cohort of CKD Stages 4 and 5 patients were to describe the main characteristics of the different patterns of progression, analyse the major determinants of the rate of decline of renal function and investigate potentially modifiable factors that could influence on CKD progression.

Materials and methods

This was a longitudinal, retrospective observational study in an incident cohort of adult patients with CKD Stages 4 and 5 not on dialysis, who were admitted to our CKD outpatient clinic between January 2000 and December 2014 due to progressive decline of kidney function.

The inclusion criterion was: having at least three consecutive measurements of estimated GFR (eGFR) in a follow-up period >3 months. Patients with recent acute kidney injury or those with glomerular diseases or vasculitis under immunosuppressive therapy were excluded.

Demographic features, clinical parameters and prescribed medication were obtained from medical records. Davies comorbidity index [14] at the time of the study entry was used to categorize the aggregated diagnosis of comorbid conditions into three subgroups: absence, mild-moderate or severe.

Baseline biochemical parameters included for descriptive purposes were: haemoglobin, serum creatinine, uric acid, calcium, phosphate, bicarbonate, parathyroid hormone, albumin, haemoglobin A1c (only in diabetic patients), high-sensitivity C-reactive protein levels (data available in 675 patients) and 24-h urinary protein excretion (g/g creatinine). All measurements were performed in the same central laboratory of our hospital using standard biochemical methods. The abbreviated Modification of Diet in Renal Disease equation (MDRD) was used to estimate GFR (eGFR) [15].

Patients were followed regularly every 30–90 days. Decline in renal function was estimated as the slope of the individual

linear regression line of eGFR over follow-up time, expressed as $\pm \text{mL/min}/1.73 \text{ m}^2/\text{year}$. Negative or positive values of this parameter indicate renal disease progression or renal function improvement, respectively.

The best-fitting model of eGFR over individual follow-up time was determined in each patient for defining the pattern of CKD progression. The following models were considered: linear, quadratic and cubic. An automatic curve estimation procedure was used, and we assessed model performance by F-value and the coefficient of determination (R^2).

When the relationship between eGFR over time did not fit any statistical significance model ($P \geq 0.05$), the pattern of CKD progression was considered as 'unidentifiable' (Figure 1A); when the best-fitting model was linear, the pattern of progression was considered as 'linear' (Figure 1B); when the best-fitting model was curvilinear (quadratic or cubic), the pattern was considered as 'nonlinear' (Figure 1C–E). Finally, all positive slopes were considered as 'positive pattern' or renal function improvement (Figure 1F).

Study design and statistical methods

This was a retrospective observational study in which demographic, clinical and biochemical characteristics of patients were described according to the pattern of CKD progression.

The main determinants of CKD progression were analysed using multiple linear regression models. In addition, multiple logistic regression models were also utilized to analyse associations between covariates and the velocity of CKD progression using a categorical variable. We used the arithmetic mean of eGFR slope of the whole study group as the cutoff value, and considered slow or fast progression if each individual eGFR slope was higher or lower than this value, respectively.

The most common medications used in these patients were included in the description of progression patterns and as covariates in multivariable analyses.

The following medications were included: diuretics, angiotensin-converting enzyme inhibitors (ACEIs) or

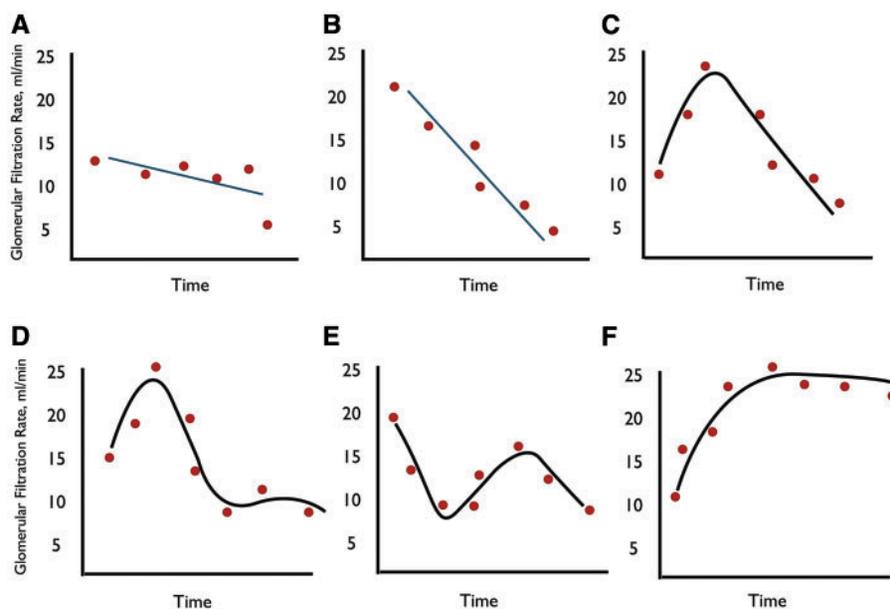


Fig. 1. Example plots illustrating the different patterns of CKD progression. (A) Unidentifiable pattern in which the relationship between eGFR over time does not fit any significant linear or curvilinear pattern. (B) Linear pattern. (C) Nonlinear quadratic pattern. (D) and (E) Nonlinear cubic pattern. (F) Positive pattern with sustained improvement of renal function.

angiotensin II receptor blockers (ARBs), dual blockade (concomitant treatment with two of the following drugs: ACEI, ARB or aliskiren), β -blockers, calcium-channel blockers, statins and antiplatelet drugs.

We also included a covariate that we called 'major treatment modifications' (MTM), which integrated some modifications of treatment performed at baseline. These changes consisted of discontinuation of vitamin D analogues and/or fibrates and/or allopurinol (this latter medication only in patients with suspected allopurinol hypersensitivity syndrome).

The rates of all-cause hospitalization during the study period were also included in the descriptive analysis, as an indicator of clinical instability.

Other therapeutic measures such as dietary protein restriction, prevention of contrast-induced nephropathy and avoidance of other potential nephrotoxic drugs, treatment with sodium bicarbonate to correct metabolic acidosis, erythropoiesis-stimulating agents to reverse anaemia and measures to control serum phosphate (diet and/or binders) were not included as covariates in the multivariate analysis, although these treatments were indicated to all who required them.

The rest of the covariates included in the multivariate analysis were: age, sex, comorbidity index, current smoking, diabetes mellitus, systolic and diastolic blood pressure measured at the first visit, baseline eGFR and urinary protein excretion.

Due to the long study period, and in an attempt to adjust the hypothetical improvement over time in practice management and treatment guidelines, we also included a variable in which points were allocated to each one of the three consecutive 5-year study periods. Thus, the early period (2000–04) received 1 point, the mid-period (2005–09) 2 points and the late period (2010–14) 3 points.

Cox proportional hazards regression models were used to analyse the main determinants of death before dialysis had been initiated. The proportional hazard assumption was checked graphically (log-log Kaplan-Meier curves) for all covariates.

To estimate the cumulative incidence for requiring dialysis therapy while accounting for the competing risks of dying before dialysis initiation, a competing-risk proportional hazards regression model was built using the method of Fine and Gray, according to Putter et al.'s description [16]. The same covariates selected in the Cox model were also re-analysed with the competing-risk model, and the sub-distribution hazard ratios were estimated.

Parametric and non-parametric tests were chosen as appropriate for descriptive comparisons of continuous variables, and chi-squared test for categorical variables.

Descriptive statistics are presented as mean and standard deviation, or median and interquartile ranges (IQR) for continuous variables, and absolute values and percentages for categorical variables. A $P < 0.05$ was considered to be significant. All P -values are reported two-sided. Analyses were performed using IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA), and STATA 11.1 (StataCorp, College Station, TX, USA).

Results

Patients

During the study period, data were retrieved from 1383 patients, of whom 944 patients fulfilled the inclusion criteria, and 29 were excluded as they were found to have recent acute kidney injury or were under immunosuppressive therapy for primary

glomerulonephrities or vasculitis. Thus, the study group consisted of 915 patients, whose demographic, clinical and biochemical characteristics are detailed in Table 1.

CKD progression

The mean eGFR slope in the overall sample was: -3.35 ± 4.44 mL/min/1.73 m²/year. This parameter followed a Gaussian distribution (Figure 2) with a minimum and maximum values of -25.5 and $+15.5$ mL/min/1.73 m²/year, respectively.

Mean eGFR slopes were consistently improving over the study periods (early, mid and late): -3.81 ± 4.03 versus -3.35 ± 4.28 versus -2.74 ± 5.08 mL/min/year, respectively [$P = 0.016$, analysis of variance (ANOVA)].

Patterns of progression of CKD

In all, 349 patients (38%) showed a linear pattern of CKD progression. In 213 patients (23%), the regression between eGFR over time did not fit any statistical significant pattern (unidentifiable pattern). In 215 patients (24%), the best-fitted model was nonlinear (curvilinear), while the remaining 138 patients (15%) showed improvement of renal function (positive pattern).

The nonlinear progression pattern consisted of 100 patients with quadratic and 115 with cubic curves.

Main characteristics of patients according to CKD progression patterns

Tables 1 and 2 show the main characteristics of patients according to CKD progression patterns.

Of note, patients with the unidentifiable pattern had the shortest follow-up time and the lowest number of kidney function measurements (overall median of five determinations). Patients with unidentifiable and positive patterns were older, and exhibited greater numbers of comorbid conditions and hospitalization rates.

The slope of CKD progression was steeper (faster progression) in unidentifiable and linear patterns, as opposed to the group with the nonlinear pattern. Consistent with this finding, both mean systolic and diastolic blood pressure, and urinary protein excretion were higher in the unidentifiable and linear patterns than in the nonlinear pattern.

Dual blockade of the renin-angiotensin system (RAS) was prescribed more frequently in patients with unidentifiable or linear CKD progression patterns. The mean eGFR slope of the 79 patients on dual RAS blockade was significantly steeper than that of the rest of the study patients (-6.06 ± 5.36 versus -3.09 ± 4.27 mL/min/1.73 m²/year, $P < 0.0001$).

MTM were more frequently performed among patients with renal function improvement (19%). The mean eGFR slope in the 93 patients in whom one or more drugs suspected to be involved in the decline of kidney function were discontinued, was more favourable than that of the rest of the study patients (-2.06 ± 3.98 vs -3.49 ± 4.47 mL/min/1.73 m²/year, $P = 0.003$). More specifically, the mean eGFR slope of the 58 patients who discontinued vitamin D analogues was: -2.26 ± 3.69 mL/min/1.73 m²/year; 30 patients who discontinued fibrates: -1.82 ± 3.93 mL/min/1.73 m²/year; and 9 patients in whom allopurinol was withdrawn: -1.61 ± 5.30 mL/min/1.73 m²/year.

The aetiologies of CKD according to the pattern of progression are detailed in Table 1. No significant differences were found in the frequency distribution of aetiologies, although it is worth mentioning the low percentage of diabetic nephropathy among patients with patterns associated with slower

Table 1. Demographic, clinical characteristics and outcome of the whole study group, and according to CKD progression patterns

Variable	Total	Unidentifiable	Linear	Nonlinear	Positive	P ^a
Patients (%)	915	213 (23)	349 (38)	215 (24)	138 (15)	
Age, years (SD)	65 (14)	67 (13)	63 (15)	64 (14)	70 (13)	<0.0001
Sex, men (%)	475 (52)	118 (55)	163 (47)	114 (53)	80 (58)	0.073
Body mass index, kg/m ² (SD)	29.5 (5.9)	30.2 (6.1)	29.3 (5.8)	29.2 (5.9)	29.6 (5.3)	0.234
Current smokers	157 (17)	33 (16)	63 (18)	42 (20)	19 (14)	0.461
Comorbidity index	380 (41)/	67 (32)/	169 (48)/	101 (47)/	43 (31)/	<0.0001
(absence/mild-moderate/severe)	445 (49)/	118 (55)/	152 (44)/	100 (46)/	75 (54)/	
Diabetes mellitus	90 (10)	28 (13)	28 (8)	14 (7)	20 (15)	
Diabetes mellitus	330 (36)	101 (47)	112 (32)	70 (33)	47 (34)	0.003
Aetiology CKD						
Unknown	370 (40)	81 (38)	124 (35)	91 (42)	74 (53)	<0.0001
Glomerulonephritis	93 (10)	15 (7)	43 (12)	24 (11)	11 (8)	
Diabetic nephropathy	206 (23)	66 (31)	81 (23)	38 (18)	21 (15)	
Interstitial	110 (12)	24 (11)	40 (12)	30 (14)	16 (12)	
APKD	71 (8)	13 (6)	41 (12)	14 (6)	3 (2)	
Ischaemic	45 (5)	10 (5)	13 (4)	10 (5)	12 (9)	
Others	20 (2)	4 (2)	7 (2)	8 (4)	1 (1)	
Systolic blood pressure, mmHg	158 (27)	162 (28)	161 (27)	155 (24)	147 (25)	<0.0001
Diastolic blood pressure, mmHg	87 (14)	87 (14)	89 (14)	87 (14)	81 (14)	<0.0001
Baseline eGFR, mL/min/1.73 m ²	14.7 (4.5)	14.0 (4.4)	15.1 (4.3)	14.8 (4.8)	14.6 (4.9)	0.063
Mean follow-up time, months	23.2 (21.9)	13.9 (14.3)	22.8 (19.6)	31.0 (25.5)	26.8 (25.7)	<0.0001
Number of samples (median, IQR)	7 (5–11)	5 (4–7)	8 (5–12)	10 (7–14)	6 (4–10)	<0.0001
eGFR slope, mL/min/1.73 m ² /year	-3.35 (4.44)	-4.07 (4.41)	-5.26 (3.96)	-3.19 (2.62)	+2.36 (2.87)	<0.0001
Hospitalization rate, days/year	3.1 (6.7)	6.3 (9.1)	1.6 (4.5)	1.6 (3.8)	4.1 (8.2)	<0.0001
Dialysis initiation	583 (64)	125 (59)	271 (78)	162 (75)	25 (18)	<0.0001
Death before dialysis initiation	142 (16)	41 (19)	37 (11)	30 (14)	35 (25)	<0.0001
Lost to follow-up	14 (2)	3 (1)	0 (0)	2 (1)	9 (7)	<0.0001

^aANOVA or chi-square inter-groups.

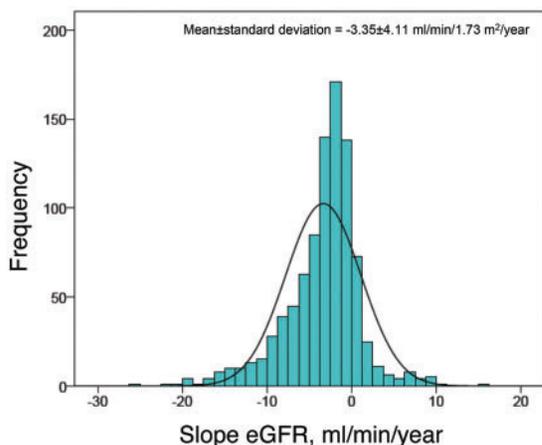


Fig. 2. Histogram representing frequency distribution of eGFR slopes in the whole study group.

progression (nonlinear and positive), and the predominance of unknown aetiology and atherosclerotic vascular disease among patients with the positive pattern.

In diabetic patients, levels of haemoglobin A1c did not significantly differ across the four different patterns of CKD progression (Table 2).

Median C-reactive protein levels were higher in patients with unidentifiable and positive patterns (Table 2), consistent with their respective comorbidity burden.

Factors associated with faster CKD progression

By multiple linear regression analysis, the best determinants of eGFR slope are shown in Table 3. Covariates associated with slower progression were: age (slower progression in ageing patients), and discontinuation of drugs suspected to be involved in kidney function decline. On the contrary, higher systolic blood pressure, the magnitude of urinary protein excretion and the treatment with dual RAS blockade were associated with faster progression.

These same covariates determined the best predictive equation for faster progression of CKD defined as eGFR slope lower than the mean value of the whole study group (Table 4).

In diabetic patients, mean levels of haemoglobin A1c were almost identical in fast and slow progressors ($6.73 \pm 1.32\%$ versus $6.73 \pm 1.49\%$, respectively). Haemoglobin A1c levels did not correlate with eGFR slopes ($\beta = 0.012$; $P = 0.830$).

Median C-reactive protein levels were similar in slow and in fast progressors (3.65 versus 3.48 mg/L, $P = 0.840$ Mann-Whitney test). C-reactive protein levels correlated weakly but significantly with eGFR slopes in a univariate model ($\beta = 0.085$; $P = 0.027$). However, C-reactive protein levels no longer remained significantly associated with eGFR slopes when demographic characteristics were included in a multivariate model ($\beta = 0.072$; $P = 0.061$).

Determinants of worse outcomes (death or need for dialysis)

During a median follow-up period of 16 months (IQR: 8–30 months), 583 patients initiated dialysis (64%), and 142 patients died before dialysis had been initiated (16%).

By Cox proportional hazards regression model, the main determinants of mortality before dialysis initiation, and of

Table 2. Baseline biochemical characteristics and main treatments of the whole study group, and according to CKD progression patterns

Variable	Total	Unidentifiable	Linear	Nonlinear	Positive	P ^a
Baseline biochemical parameters						
Haemoglobin, g/dL	11.4 (4.3)	11.7 (8.4)	11.3 (1.7)	11.5 (1.4)	11.5 (1.9)	0.696
Serum uric acid, mg/dL	7.6 (1.9)	7.6 (1.9)	7.3 (1.9)	7.9 (1.9)	7.7 (2.3)	0.015
Serum total calcium, mg/dL	9.2 (0.8)	9.1 (0.9)	9.2 (0.7)	9.4 (0.8)	9.3 (0.7)	<0.0001
Serum phosphate, mg/dL	4.7 (1.0)	4.8 (1.1)	4.6 (0.9)	4.8 (1.1)	4.4 (1.1)	0.014
Serum bicarbonate, mmol/L	21.4 (4.0)	21.2 (4.3)	21.2 (3.8)	21.8 (3.9)	22.3 (4.3)	0.031
Haemoglobin A _{1c} in diabetic patients, %	6.73 (1.42)	6.72 (1.32)	6.77 (1.47)	6.92 (1.56)	6.39 (1.28)	0.260
Serum albumin, g/dL	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	3.9 (0.5)	4.0 (0.4)	0.240
Serum C-reactive protein, mg/L ^b	3.53 (1.16–9.20)	4.04 (1.65–11.50)	3.22 (1.02–8.96)	2.83 (0.87–6.87)	4.86 (1.40–13.51)	0.011
Urinary protein excretion, g/g creatinine	2.13 (2.35)	2.65 (2.76)	2.31 (2.16)	1.96 (2.45)	1.13 (1.52)	<0.0001
Treatments						
Successful arterial-venous fistulae	283 (31)	61 (29)	137 (39)	67 (32)	18 (13)	<0.0001
Diuretics	595 (65)	142 (67)	209 (60)	155 (72)	89 (65)	0.029
ACEI or ARB	693 (76)	170 (80)	275 (79)	157 (73)	91 (66)	0.008
Dual RAS blockade (ACEI + ARB)	79 (9)	18 (9)	40 (12)	17 (8)	4 (3)	0.020
β-blockers	208 (23)	56 (26)	73 (21)	45 (21)	34 (25)	0.412
Calcium-channel blockers	441 (48)	104 (49)	175 (50)	101 (47)	61 (44)	0.665
Antiplatelet drugs	305 (33)	81 (38)	102 (29)	38 (32)	54 (39)	0.068
Statins	438 (48)	111 (52)	171 (49)	94 (44)	62 (45)	0.299
MTM ^c	93 (10)	28 (13)	25 (7)	14 (7)	26 (19)	<0.0001

^aANOVA or chi-square inter-groups.

^bData available in 675 patients, expressed as median and interquartile ranges, and compared by Kruskal–Wallis test.

^cMTM: discontinuation of vitamin D analogues, fibrates and/or allopurinol (only in patients with suspected allopurinol hypersensitivity) at baseline.

Table 3. Multiple linear regression model for eGFR slope (mL/min/1.73 m²/year)

Variable	B coefficient	95% CI B coefficient	β	P
Age, years	0.045	0.026; 0.064	0.142	<0.0001
Sex, male = 1	−0.615	−1.136; −0.094	−0.069	0.021
Study periods; early = 1, mid = 2, late = 3	0.368	0.034; 0.701	0.066	0.031
Systolic blood pressure, × cmHg	−0.225	−0.325; −0.125	−0.137	<0.0001
Proteinuria, g/g creatinine	−0.630	−0.745; −0.514	−0.333	<0.0001
Dual RAS blockade (0, 1)	−1.475	−2.424; −0.526	−0.093	0.002
MTM ^a (0, 1)	1.290	0.420; 2.161	0.088	0.004
Constant	−1.794	−3.723; 0.136		

Not in equation: comorbidity index, diabetes mellitus, baseline eGFR, smokers, diastolic blood pressure, diuretics, ACEI or ARB treatment, β-blockers, calcium-channel blockers, antiplatelet drugs, statins.

^aMTM: discontinuation at baseline of vitamin D analogues, fibrates and/or allopurinol (only in patients with suspected allopurinol hypersensitivity).

dialysis initiation adjusted for competing risk of death, are shown in Table 5.

Summarizing these results, patients who died before dialysis had been initiated were characterized by the following clinical profile: ageing patient with high degree of comorbidity, current smoker, with proteinuric renal disease, but treated less frequently with ACEI or ARB. On the other hand, the most notable characteristics of patients who needed earlier initiation of dialysis were as follows: younger male with lower baseline renal function, higher systolic blood pressure and proteinuric renal disease (more common diabetic), treated more frequently with dual blockaded of RAS and/or β-blockers.

Figure 3 shows 'survival without dialysis' curves according to the pattern of CKD progression, and Figure 4 shows 'survival without dialysis' curves according to the rate of CKD progression (faster or slower).

Discussion

In this observational study, four different patterns of CKD progression could be distinguished: unidentifiable, linear, nonlinear and positive.

The unidentifiable pattern, in which the relationship between eGFR over time did not fit any predictable pattern, accounted for 23% of the study patients. These patients were older, had greater comorbidity, especially diabetes mellitus, higher systolic blood pressure and urinary protein excretion, and they had the worst outcomes (faster CKD progression and lesser survival rate with no dialysis).

A more frequent general frailty and clinical instability in these patients, as reflected by their greater comorbidity index and hospitalization rate, may explain this unpredictable pattern of CKD progression. These patients usually present abrupt changes in their clinical course and kidney function, mainly related to cardiovascular (congestive heart failure) and infectious complications that result in hospitalization, and they eventually need the initiation of unplanned dialysis. The shorter follow-up time in this group could also influence the lack of a clearly defined pattern of CKD progression.

Although the linear pattern of CKD progression was the most common, it accounted for only 38% of the study patients. Some characteristics of these patients, such as higher systolic blood pressure and urinary protein excretion, matched those exhibited by patients with the unidentifiable pattern. However,

patients with the linear pattern were younger and had fewer comorbidities than those with the unidentifiable pattern. In addition, primary glomerulonephrities and adult polycystic kidney disease (APKD) were the predominant CKD aetiologies in this group.

The linear pattern was also associated with faster decline of kidney function and earlier need for dialysis initiation. Among the potential factors involved, dual RAS blockade treatment was more commonly prescribed in these patients, and although some concerns about confounding by indication should be considered, dual RAS blockade treatment was significant and independently associated with faster CKD progression in adjusted multivariate analyses.

Associations between dual RAS blockade treatment and faster CKD progression have already been described in other studies, in patients both with and without diabetic nephropathy [17–19], and although these results should be interpreted cautiously, it would be advisable to take them into consideration when this therapy is indicated to patients with advanced CKD.

Table 4. Multiple logistic regression model for faster CKD progression

Variable	Odds ratio	95% CI odds ratio	P
Age, years	0.980	0.970; 0.990	<0.0001
Sex, male = 1	1.401	1.045; 1.879	0.024
Systolic blood pressure, ×10 mmHg	1.081	1.021; 1.144	0.008
Proteinuria, g/g creatinine	1.413	1.301; 1.534	<0.0001
Treatment with dual RAS blockade (0, 1)	2.163	1.268; 3.689	0.005
MTM ^a (0, 1)	0.445	0.259; 0.764	0.003

Not in equation: study periods, smoking, diastolic blood pressure, baseline eGFR, diabetes, comorbidity index, diuretics, ACEI or ARB therapy, β-blockers, calcium-channel blockers, antiplatelet drugs, statins.

^aMTM: discontinuation at baseline of vitamin D analogues, fibrates and/or allopurinol (only in patients with suspected allopurinol hypersensitivity).

The nonlinear pattern of CKD progression was also common—24% of patients. Despite the scant differences in clinical characteristics of patients with linear and nonlinear patterns, those with the nonlinear pattern showed a slower decline of renal function. The unsteady CKD progression in the nonlinear pattern may be explained by transient or partial response to the numerous therapeutic interventions performed to these patients, which may eventually help to delay the need for dialysis.

The positive pattern or renal function improvement was observed in 15% of the study patients. These patients were older and had higher degrees of comorbidity; however, mean blood pressure and proteinuria were the lowest compared with those of the rest of the groups. Interestingly, these patients were being treated less frequently with ACEI or ARB or dual RAS blockade, and in 19% of them MTM were performed at baseline.

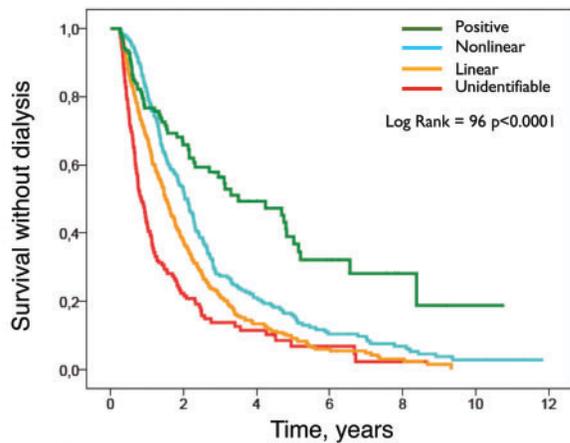
Vitamin D analogues, fibrates and allopurinol are drugs commonly prescribed in CKD patients that can be associated with real [20–23] or apparent decrease of renal function due to misinterpretations of eGFR from equations based on serum creatinine measurements [24, 25]. Well aware of this potential adverse effect, we decided long ago to discontinue these drugs in a systematic manner to all patients admitted to our CKD clinic (allopurinol was only stopped in cases in which hypersensitivity to this medication was suspected). This intervention, which we called MTM, was performed in ~10% of the study patients, and this covariate resulted to be independently associated with a more favourable CKD progression in multivariable analyses.

During the followed-up period, almost two-thirds of the study patients needed dialysis, 16% died before dialysis had been initiated and 20% had a favourable outcome—survival without dialysis or kidney transplantation.

As would be expected, baseline kidney function and factors associated with more rapid CKD progression (higher blood pressure and urinary protein excretion) were the best determinants of the need for dialysis adjusted for the competing risk of dying

Table 5. Cox proportional hazard regression model for association between covariates and mortality before dialysis initiation, or dialysis initiation adjusted for competing risk of death (sub-distribution hazards model of Fine and Gray)

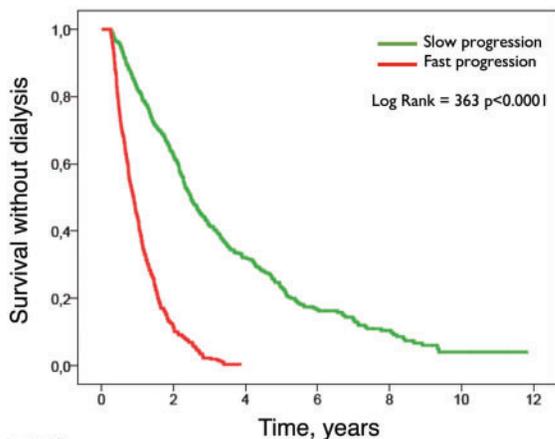
Variable	Mortality			Dialysis initiation		
	Hazard ratio	95% CI hazard ratio	P	Sub-hazard ratio	95% CI sub-hazard ratio	P
Age, years	1.096	1.071; 1.123	<0.0001	0.978	0.971; 0.985	<0.0001
Sex, male = 1	1.342	0.914; 1.968	0.133	1.397	1.161; 1.686	<0.0001
Comorbidity index (0, 1, 2)	1.955	1.425; 2.681	<0.0001	0.805	0.651; 0.995	0.045
Study periods, Early = 1; Middle = 2; Recent = 3	1.005	0.761; 1.325	0.972	0.892	0.783; 1.014	0.082
Current smokers (0, 1)	2.485	1.514; 4.078	<0.0001	0.862	0.676; 1.098	0.228
Systolic blood pressure, ×10 mmHg	1.045	0.972; 1.124	0.235	1.058	1.020; 1.098	0.002
Baseline eGFR, ml/min/1.73 m ²	0.951	0.913; 0.990	0.015	0.877	0.856; 0.899	<0.0001
Proteinuria, g/g creatinine	1.254	1.174; 1.339	<0.0001	1.105	1.053; 1.159	<0.0001
Diabetes mellitus (0, 1)	1.209	0.812; 1.799	0.350	1.323	1.030; 1.700	0.028
Diuretics (0, 1)	1.408	0.952; 2.082	0.086	1.051	0.872; 1.265	0.602
ACEI or ARB treatment (0, 1)	0.574	0.389; 0.847	0.005	1.002	0.788; 1.273	0.989
Dual blockade RAS (0,1)	0.601	0.236; 1.532	0.286	1.333	1.005; 1.768	0.046
β-blockers (0, 1)	1.113	0.727; 1.703	0.622	1.291	1.038; 1.606	0.022
Calcium-channel blockers (0, 1)	0.705	0.486; 1.024	0.066	1.162	0.970; 1.392	0.103
Antiplatelets (0, 1)	1.086	0.764; 1.544	0.645	0.852	0.691; 1.052	0.136
Statins (0, 1)	0.861	0.595; 1.246	0.427	1.118	0.929; 1.346	0.238
MTM (0, 1)	0.134	0.018; 0.966	0.046	0.974	0.748; 1.268	0.846



Patients at risk

Positive	138	57	24	11	3	1
Nonlinear	215	109	38	16	9	3
Linear	349	117	37	12	4	
Unidentifiable	213	29	9	3	1	

Fig. 3. Kaplan-Meier 'survival without dialysis' curves according to different patterns of progression.



Patients at risk

Fast progression	370	36				
Slow progression	545	276	108	42	17	4

Fig. 4. Kaplan-Meier 'survival without dialysis' curves according to the rate of progression of CKD (faster or slower).

before dialysis initiation. While the treatment with either ACEI or ARB seemed to be associated with less mortality, the concomitant prescription of both drugs (dual blockade of RAS) or the use of β -blockers was significantly associated with earlier need of dialysis.

In this study, a high proportion of elderly patients showed a slow CKD progression. Nearly two-thirds (64%) of the study patients over 65 years of age showed less steep eGFR slopes (greater than $-3.35 \text{ mL}/\text{min}/1.73 \text{ m}^2/\text{year}$). This finding has already been described in previous studies [26–28], although the causal link between ageing and slow CKD progression remains elusive. One explanation widely supported is that 'ageing kidney' and its associated outcome characteristics [29] could be the predominant aetiology of renal function impairment in a high proportion of elderly CKD patients. Besides, other clinical characteristics and confounders related with ageing, such as better compliance with prescribed medication and dietary advice (authors' subjective perception), fewer current smokers

and inaccuracy of creatinine-based estimations of GFR, may also influence the rate of renal function decline in our elderly CKD population.

One important conclusion that can be drawn from these results is that renal function decline at later stages of CKD is not uniformly linear, and the velocity of the progression can vary widely. Thus, the characteristics associated with these different patterns of CKD progression should be considered in clinical studies and trials recruitment, and from a clinical practice standpoint, for proper planning and scheduling of the initiation of dialysis or pre-emptive kidney transplantation.

Potential limitations of this study need to be acknowledged. Due to the observational and retrospective nature of the study no causal relationships could be established. The study was single centre, and the overall outcomes and kidney function could be highly influenced by the treatment protocols of our clinic, thus limiting the reproducibility of some of the results from this study.

Renal function was not measured by gold standard methods. The precision and accuracy of creatinine-based formulas for estimating the renal function can be affected by numerous factors, which may eventually influence the estimation of CKD progression observed in this study.

In conclusion, this study shows that, in addition to highly expected risk factors for CKD progression (age, sex, arterial hypertension, proteinuria), other potential modifiable factors, mainly related to the adverse effects of commonly prescribed medication, may influence significantly the rate of renal function decline of CKD patients at later stages. Interactions among these factors result in different patterns of progression, the identification of which may be useful for optimizing the care of patients with advanced CKD.

Conflict of interest statement

None declared.

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