PATTERNS OF PROGRESSION OF CHRONIC KIDNEY DISEASE AT LATER STAGES

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Introduction and Aims

◆ At later stages of chronic kidney disease (CKD), a pattern of linear and irreversible renal function decline is thought to be the most common. However, recent observational studies have shown that the patterns of CKD progression may be highly heterogeneous, and trajectories of glomerular filtration rate (GFR) over time can fit patterns different from linear.

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

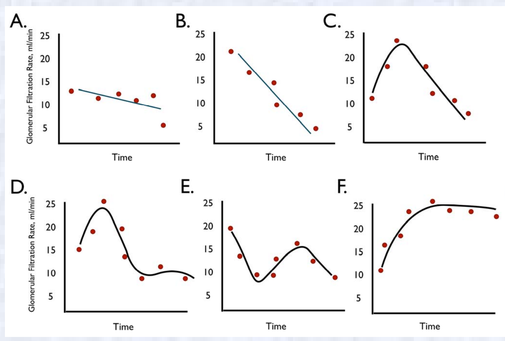
◆ Aims: To describe the characteristics of the different patterns of CKD progression, and to investigate potentially modifiable factors associated with the rate of decline of renal function.

Patients and Methods

◆ Longitudinal, retrospective observational study in an incident cohort of adult patients with CKD stage 4-5 not on dialysis, who were admitted to our CKD outpatient clinic between January 2000 and December 2014 due to progressive decline of kidney function. Decline in renal function was estimated as the slope of the individual linear regression line of eGFR over time, expressed as ± ml/min/1.73 m^2/year.

◆ Inclusion criteria were: having at least three consecutive measurements of eGFR in a follow-up period longer than three months. Patients with recent acute kidney injury or those with glomerular diseases or vasculitis under immunosuppressive therapy were excluded.

◆ When the relationship between eGFR over time did not fit any statistical significance model, 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, D, E). Finally, all positive slopes were considered as 'positive pattern' or renal function improvement (figure 1F).



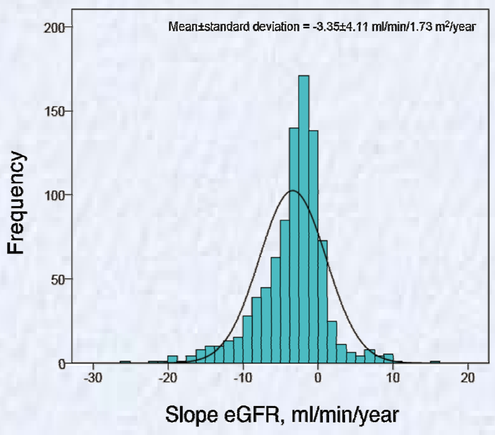
◆ The most common medications used in these patients were included in the description of progression patterns and as covariates in multivariable analyses. We also included a covariate that we called it «major treatment modifications» (MTM), of discontinuation of vitamin D analogues, and/or fibrates, and/or allopurinol.

◆ Cox proportional hazards regression models were used to analyze the main determinants of death before dialysis had been initiated. 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 description. The same covariates selected in the Cox model were also re-analyzed with the competing risk model, and the sub-distribution hazard ratios were estimated.

Results

Clinical characteristics and outcomes of the study group, and according to CKD progression patterns

Variable	Total	Unidentifiable	Linear	Nonlinear	Positive	P
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, %						
Absence	380 (41)	67 (32)	169 (48)	101 (47)	43 (31)	<0.0001
Mild-moderate	445 (49)	118 (55)	152 (44)	100 (46)	75 (54)	
Severe	90 (10)	28 (13)	28 (8)	14 (7)	20 (15)	
Diabetes mellitus	330 (36)	101 (47)	112 (32)	70 (33)	47 (34)	0.003
Etiology CKD						
Unknown	370 (40)	81 (38)	124 (35)	91 (42)	74 (53)	<0.0001
Glomerulonephrities	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)	
Ischemic	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, I.Q ranges)	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



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

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

Variable	Total	Unidentifiable	Linear	Nonlinear	Positive	P
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
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
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
Betablockers	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
Major Treatment Modification	93 (10)	28 (13)	25 (7)	14 (7)	26 (19)	<0.0001

Multiple linear regression model for eGFR slope (ml/min/1,73 m^2/ year)

Variable	B coefficient	C.I. 95% B coefficient	Beta	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, x cm Hg	-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
Major treatment modifications, (0,1)	1.290	0.420; 2.161	0.088	0.004
Constant	-1.794	-3.723; 0.136		

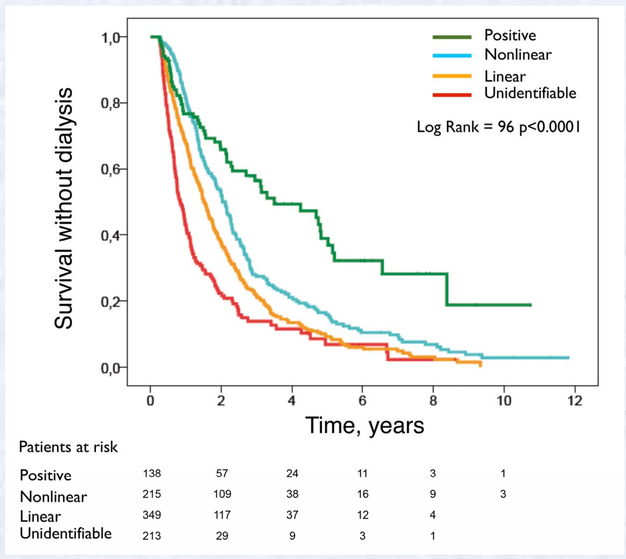
Multiple logistic regression model for faster CKD progression

Variable	Odds ratio	95% C.I. 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, x 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
Major treatment modifications, (0,1)	0.445	0.259; 0.764	0.003

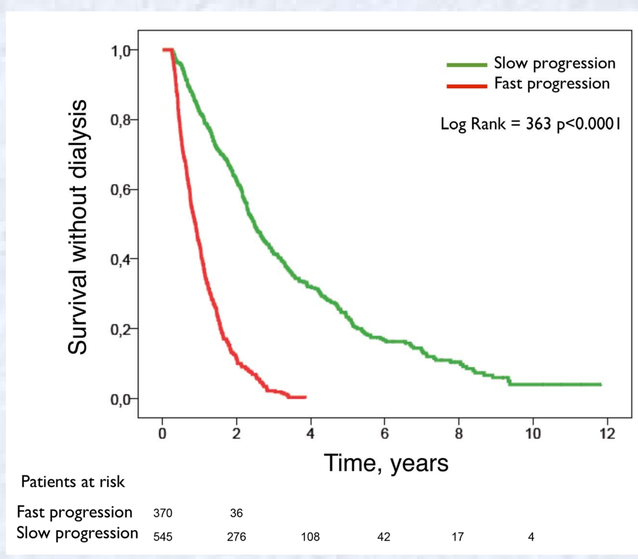
Cox proportional hazard regression model for association between covariates and mortality before dialysis initiation, or dialysis initiation adjusted for competing-risk of death

Variable	Mortality Hazard ratio	Mortality 95% C.I. Hazard ratio	Mortality p	Dialysis initiation Sub-hazard ratio	Dialysis initiation 95% C.I. Sub-hazard ratio	Dialysis initiation 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, x10 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
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
Beta-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
Major treatment modifications, (0,1)	0.134	0.018; 0.966	0.046	0.974	0.748; 1.268	0.846

Kaplan-Meier survival without dialysis curves according to different patterns of progression



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



Conclusions

◆ 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 on the rate of renal function decline of CKD patients at later stages. Interactions among these factors result in different patterns of progression, whose identification may be useful for optimizing the care of patients with advanced CKD.

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