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A clinical stratification tool for chronic kidney disease progression rate based on classification tree analysis

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ABSTRACT

Background. Registry-based studies have identified risk factors for chronic kidney disease (CKD) and for progression to end-stage renal disease. However, usually, these studies do not incorporate sequential measurements of kidney function and provide little information on the prognosis of individual patients. The aim of this study is to identify which combinations of demographic and clinical characteristics are useful to discriminate patients with a differential annual decline in glomerular filtration rate (GFR).

Methods. This observational retrospective study includes patients enlisted in the registry of the Prevention of Progressive Renal Insufficiency Project of Emilia-Romagna region (Italy) from July 2004 to June 2010, with at least four serum creatinine measurements. Classification tree analysis (CTA) was used to identify subgroups of patients with a different annual GFR decline using demographic and laboratory data collected at study entry.

Results. The CTA procedure generated seven mutually exclusive groups. Among patients with proteinuria, those with a baseline estimated GFR (eGFR) of >33 mL/min/1.73 m^2 exhibited the fastest illness progression in the study population (−3.655 mL/min/1.73 m^2), followed by patients with a baseline eGFR of <33 mL/min/1.73 m^2 and a baseline serum phosphorus of >4.3 mg/dL (−2.833 mL/min/1.73 m^2). Among patients without proteinuria, those aged <67 years exhibited a significantly faster progression, which was even faster for the subgroup with diabetes. Among patients aged >67 years, females had on average a stable eGFR over time, with a large variability.

Conclusions. It is possible to rely on a few variables typically accessible in routine clinical practice to stratify patients with a different CKD progression rate. Stratification can be used to guide decisions about the follow-up schedule, treatments to slow progression of kidney disease, prevent its complications and to begin planning for dialysis and transplantation.

Keywords: CKD progression, decision tree, prediction models

ORIGINAL ARTICLE

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem, with an estimated lifetime risk of >50%, higher than that for diabetes, invasive cancer and coronary heart disease [1], and a prevalence of 20.3% in the USA and 13.2% in the Italian general population aged >40 years [2]. The past decade has witnessed an increasing focus on CKD and its complications, which has led to an improved understanding of their impact on health-care resources. Moreover, since the publication of the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for the classification of CKD and the availability of screening for kidney function in primary care settings [3], the waiting lists of nephrology clinics have increased exponentially, challenging the ability of nephrologists to do a quick triage of those patients with CKD most likely to progress to end-stage renal disease (ESRD) and those who can be safely referred back to primary care physicians for monitoring and routine clinical management.

Prospective epidemiological and registry-based studies have identified risk factors for CKD in the general population as well as risk factors for progression to ESRD in patients with established CKD, and models using these variables have been developed that can accurately predict progression to kidney failure in patients with CKD stages 3–5 [4].

However, because these studies are focused on predictors of outcomes [death, ESRD and cardiovascular disease (CVD)] and do not incorporate sequential measurements of kidney function, they provide little information on the prognosis of individual patients [5]. A better understanding of the characteristics of patients with different rates of CKD progression would facilitate clinical management of 'slow progressors', who do not require a tight and frequent monitoring of their disease and 'fast progressors', for whom more attention of nephrologists is needed to delay renal replacement therapy.

In this paper, we propose an empirically based approach to identify subgroups of patients with a differential progression of kidney function that takes advantage of classification tree analysis (CTA). This technique has been applied in different areas of medicine, including psychiatry and health services research [6, 7], and in the present study is used in a large cohort of patients participating in the Italian Prevention of Progressive Renal Insufficiency (PIRP) project to support clinical decision-making. The aim of this study is to identify, using CTA, which combinations of demographic and clinical characteristics are useful to discriminate patients with a differential annual decline in glomerular filtration rate (GFR).

MATERIALS AND METHODS

Patients

The study population was drawn from the registry of the PIRP project. This project is a collaborative network of nephrologists and general practitioners operating in Emilia-Romagna, a region located in north-eastern Italy, with 4 351 393 inhabitants (2011 census data, National Institute of Statistics). The project is devised to delineate intervention strategies for delaying illness progression, to increase awareness of CKD complications and to optimize CKD patient care. The PIRP registry was funded by Emilia-Romagna Region starting from July 2004, to collect demographic, clinical and laboratory characteristics of all consecutive patients referred to nephrology centres by primary care physicians. Data are collected at baseline and at each follow-up visit. Exit from PIRP occurs in the event of death, dialysis, transplantation or loss to follow-up.

Records of patients who entered PIRP between 1 July 2004 and 30 June 2010 and with at least four serum creatinine measurements were extracted for the analyses. The Emilia-Romagna Region provided the linkage of patients registered in the PIRP database with the hospital discharge records database. This was done to increase the reliability of information on comorbid conditions. Loss to follow-up was defined as a period of 18 months without visits. Physical examination and collection of demographic characteristics were carried out at baseline, corresponding to the entry into the PIRP project. The observation period for the determination of the progression rate started since the first available creatinine and lasted until 30 June 2011. Measurement of serum creatinine and other biomarkers was performed in a fasting state at each study site. All laboratories use a standardized and traceable creatinine assay. Moreover, to ensure quality control, the laboratories of Emilia-Romagna region participate in a network coordinated by the British Columbia for creatinine standardization, with the aim of minimizing the bias deriving from laboratory error and from tests performed in multiple locations.

In order to allow for the limited number of patients who had complete data on laboratory tests at baseline, laboratory tests performed as close as possible to the entry date into PIRP were considered for the analyses, in a time window from 3 months before to 1 year after the baseline date. Urine proteins were coded as present if one of the following conditions was met: dipstick protein >20 mg/dL, urine total protein >0.3 g/24 h, microalbuminuria >20 mg/L and absent otherwise. Low-density lipoprotein (LDL) cholesterol level was estimated using Friedwald's formula.

Hypertension was defined as present when blood pressure (BP) was not on target (diastolic BP >90 mmHg, systolic pressure >140 mmHg) and untreated or when BP was not on target despite ongoing treatment with antihypertensives, diuretics, β-blockers, calcium channel blockers and ACE inhibitors (ATC classes C02, C03, C07, C08, C09). CVD was defined as a history of ischaemic heart disease, chronic heart failure, cardiac arrhythmia, cerebrovascular disease or peripheral vascular disease.

GFR was estimated using the CKD-epidemiology (EPI) equation, which proved to be more appropriate than the Modification of Diet in Renal Disease equation for an elderly population [8, 9]. When the PIRP project started, the nephrologist network chose to adopt a clinical and therapeutic practice based on K/DOQI guidelines [3]. This study is exempt from approval from the Local Ethics Committee, given the de-identified nature of the dataset.

Statistical analyses

CTA based on the CHAID (χ^2 automatic interaction detection) procedure was used to determine the ability of demographic and clinical characteristics to discriminate subgroups of patients with a differential decline in kidney function.

The CTA begins with selecting from the set of predictors the one that is most associated with outcomes [annual change in estimated GFR (eGFR)] and uses it to partition the population into subgroups defined by existing categories (if the variable is dichotomous or nominal) or by categories obtained through the identification of optimal cut-points continuous variables. The procedure then continues by selecting the second best predictor and so on, until no further significant improvement in the segmentation of study participants is possible or a stopping rule is met. At the end of the procedure, a grouping of cases is obtained, such that the cases are as homogeneous as possible with respect to the value of the dependent variable. Missing data are treated as a separate category and are merged to other categories or left alone by the procedure depending on their homogeneity/heterogeneity with the existing categories.

The CTA-based is represented graphically as an inverted tree. Beginning with a root node that includes all cases, the tree branches and grows iteratively until the procedure is completed. The final nodes (or the 'leaves' of the tree) comprise subgroups with a differential outcome.

Gender, age, hypertension, diabetes, cardiac disease, smoking habits (coded as non-smoker, past smoker, current smoker), body mass index (BMI) and baseline laboratory tests, including baseline serum creatinine, serum uric acid (SUA), serum phosphates, parathyroid hormone, glycaemia, triglycerides, LDL cholesterol, haemoglobin, urine proteins and diagnosis of nephropathy, were selected as potential predictors of annual decline in eGFR. Because visits are not carried out at regular times, but in relation to clinical needs, measurement of eGFR is not available at specific time points. Therefore, we estimated the annual change in eGFR in patients with at least four visits by fitting a regression line to each patient. Although recently, some authors [10] argued that the assumption of a steady nearly linear eGFR progression over a long period is inappropriate, for the follow-up period of the present study it is still tenable.

One-way analysis of variance followed by *post hoc* pairwise comparisons with the Bonferroni-adjusted probability level was used to compare the subgroups obtained with the CTA on continuous variables. The χ^2 test was used to compare categorical variables among groups. All analyses were performed using IBM SPSS Statistics, version 20.0.

RESULTS

The characteristics of the study sample are summarized in Table 1. During the index period, 2265 patients entered PIRP and had at least four creatinine measurements. The mean follow-up period was 3.6 years (SD = 1.5 years), and the median 2.8 years (IQ range 1.9–3.8 years).

The mean age was 71.1 years (SD = 12.9) and the percentage of males was 65.1%. Diabetes was present in 32.6% of patients, hypertension in 92.1% and CVD in 73.0% (Table 1); 2.5% were in CKD stages 1 or 2, 7.9% were in 3a, 29.2% in 3b, 48.8% in 4 and 11.5% in 5. The mean annual decrease in eGFR was −1.328 mL/min/1.73 m^2 (SD = 5.16) in the overall sample.

We first examined whether the study sample was representative of all the patients currently enlisted in the PIRP registry (n = 13057). Compared with patients with fewer than four creatinine determinations, those included in the analysis had a similar gender distribution (65.1 versus 64.8% male, χ^2 = 0.09, P = 0.761) and a similar proportion with diabetes (32.6 versus 32.9%, χ^2 = 0.07, P = 0.788), but were on average 2 years younger (71.1 versus 73.2, t-test = 6.80, P < 0.001) and had higher mean serum creatinine levels at baseline (2.35 ± 0.92 versus 2.10 ± 1.64 mg/dL, t-test = 6.85, P < 0.001).

The CTA was carried out using some demographic information, comorbid disease and biochemical analyses described above as potential predictors of CKD progression. Among these 17 variables, proteinuria was identified by the procedure as the most discriminative predictor of illness progression and generated the main branching of the classification tree. Patients with proteinuria exhibited a significantly higher mean annual decrease in eGFR than those without proteinuria (−2.353 versus −0.810 mL/min/1.73 m^2, F-test = 46.04, P < 0.001) (Figure 1). Among patients with proteinuria, a subsequent split was generated according to the baseline eGFR. Patients with a baseline eGFR of >33 mL/min/1.73 m^2 (n = 230, 10.2%) exhibited a significantly faster illness progression compared with those with a baseline eGFR of <33 mL/min/1.73 m^2 (−3.655 versus −1.788 mL/min/1.73 m^2, F-test = 22.13, P < 0.001). Patients with an eGFR of >33 mL/min/1.73 m^2 proved to be younger and had a poorer lipid profile compared with the rest of the patients with proteinuria (Nodes 7

Table 1. Baseline characteristics of the study population (n = 2265)

Serum creatinine, mg/dL	2.4 ± 0.9
CKD-EPI eGFR, mL/min/1.73 m^2	28.8 ± 13.0
MDRD eGFR, mL/min/1.73 m^2	29.1 ± 12.5
Age, years	71.2 ± 12.9
Female sex, %	34.9
Current cigarette smoker, %[a]	9.9
Hypertension, %	92.1
Diabetes, %	32.6
Cardiac disease, %	72.7
BMI, kg/m^2	26.8 ± 4.5
LDL cholesterol, mg/dL	111.7 ± 39.0
total cholesterol, mg/dL	190.5 ± 44.7
Triglycerides, mg/dL	150.9 ± 83.3
Glucose, mg/dL	108.5 ± 40.4
Systolic BP, mmHg	140.3 ± 28.6
Diastolic BP, mmHg	78.2 ± 10.2
PTH, pg/mL[b]	168.0 ± 141.7

Data are expressed as mean ± SD or percentages.
[a]637 patients have missing data.
[b]954 patients have missing data.
SD, standard deviation; eGFRCKD-EPI, estimated glomerular filtration rate with chronic kidney disease epidemiology collaboration formula; eGFRMDRD, estimated glomerular filtration rate with Modification of Diet in Renal Disease formula; LDL, low-density lipoprotein; PTH, parathyroid hormone.

and 8). The subgroup with a baseline eGFR of <33 mL/min/1.73 m^2 was further split according to the baseline level of serum phosphorus. Patients with a baseline serum phosphorus of >4.3 mg/dL had on average a 2-fold annual decrease in eGFR compared with those with a baseline serum phosphorus of ≤4.3 mg/dL (−2.833 versus −1.368 mL/min/1.73 m^2, *F*-test = 13.04, P < 0.001).

Among patients without proteinuria, a first split was generated based on age (>67 versus <67 years). Younger patients exhibited a significantly faster progression (*F*-test = 15.98, P < 0.001). In this group, the presence of diabetes proved to be a relevant prognostic factor. Patients with diabetes had an annual decrease in eGFR of −2.975 mL/min/1.73 m^2 versus −1.341 mL/min/1.73 m^2 in those without diabetes (*F*-test = 8.378, P < 0.001).

Among patients aged >67 years, who constitute 50% of the sample, females had a stable eGFR over time (no annual progression), while males had an estimated eGFR loss of −0.837 mL/min/1.73 m^2.

In conclusion, the CTA procedure generated seven mutually exclusive groups with a differential decline in eGFR and used only six of the potential predictors of outcomes to build the classification tree, i.e. proteinuria, age, gender, diabetes, baseline eGFR and serum phosphates. In other words, after these variables and their interaction were entered in the model, the 'excluded' predictors did not further contribute to creating homogeneous patient subgroups.

We then examined whether the classification into seven distinct groups obtained using the CTA was corroborated by

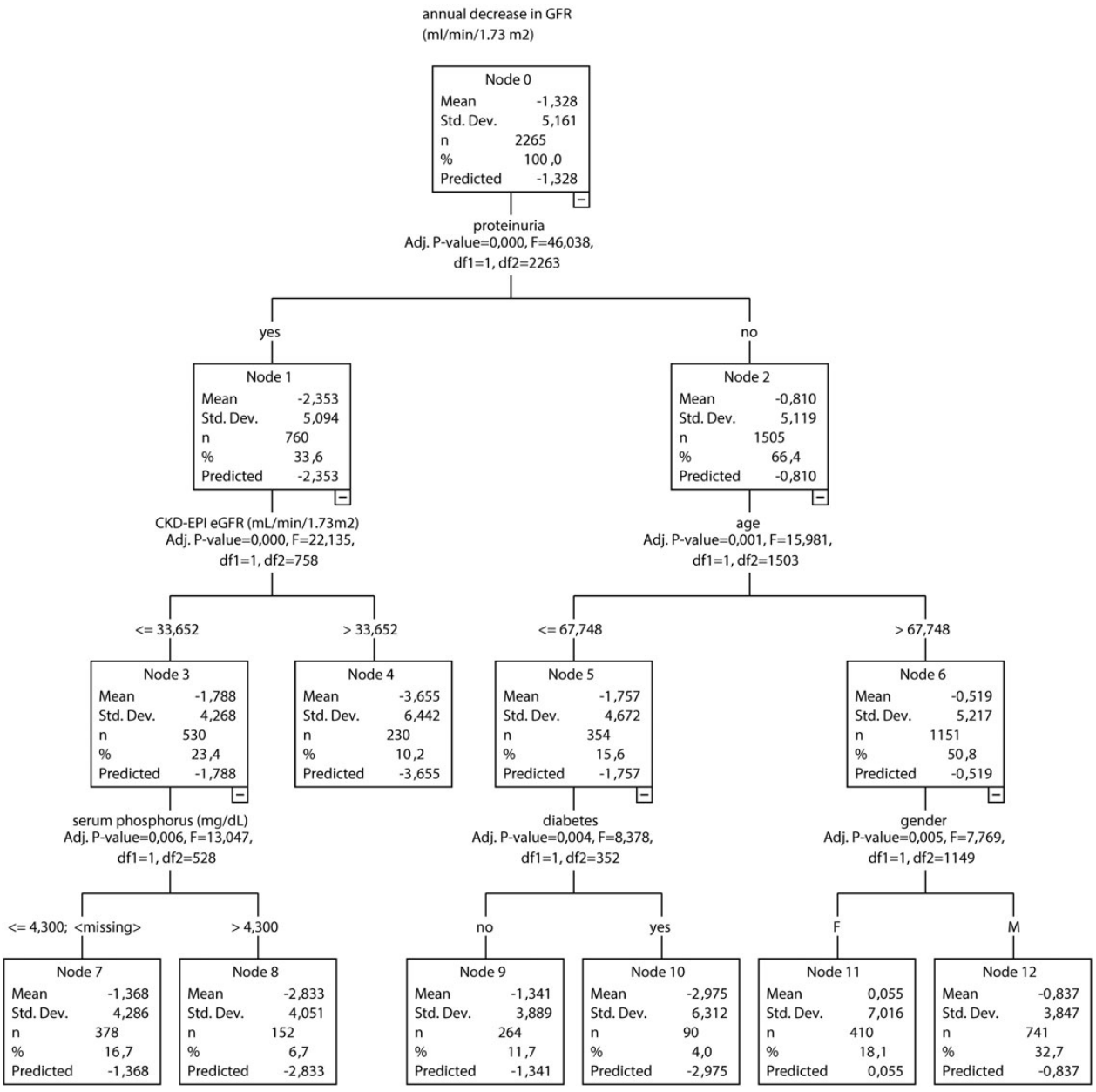

FIGURE 1: Classification tree showing subgroups with a different annual decrease in eGFR.

differences on the remaining variables used as potential predictors.

Table 2 provides the descriptive statistics of the characteristics and laboratory tests in the CTA groups and a summary of significant Bonferroni-adjusted pairwise comparisons. The CTA groups had different profiles on demographics, comorbidities and the mean level of one or more laboratory tests (except for SUA). In the tree branch including patients with proteinuria (Groups 4, 7 and 8), those with higher baseline kidney function (Group 8: eGFR >33 mL/min/1.73 m^2) were significantly younger and had higher PTH levels than those in Group 7 (eGFR ≤33 mL/min/1.73 m^2, serum phosphate >4.3 mg/dL).

Moreover, significant differences were found between the group with a GFR of ≤33 and the group with a GFR of >33 mL/min/1.73 m^2 in the type of renal disease. Specifically, glomerulonephritis was significantly more common in patients with a GFR of >33 mL/min/1.73 m^2 (23.5 versus 8.5%, $P < 0.01$) and renal vessel diseases were significantly more common in patients with a GFR of ≤33 mL/min/1.73 m^2 (35.7 versus 47.5%, $P < 0.01$), while no difference was found on other types of renal diseases.

Patients in Group 4 were younger than those in Groups 7 and 8 but exhibited higher LDL cholesterol levels.

Vice versa, in the tree branch including patients without proteinuria (Groups 9, 10, 11 and 12), Group 10 (diabetes and age <67 years, $n = 90$) proved to have the highest BMI (mean 29.5, SD = 5.92) and significantly higher levels of glycaemia and triglycerides compared with the other groups. Group 11 (females, age >67 years, $n = 410$) was characterized by a poor lipid profile.

DISCUSSION

In this study, we used CTA to stratify patients according to their CKD progression. Knowledge of the trajectory of kidney function over time in patients with specific characteristics has both clinical and methodological relevance since the decline of renal function has been reported to be a reliable indicator of cardiovascular morbidity and mortality [11–16].

To our knowledge, this is the only study that used serial measurements of GFR to build a decision tree model for patients with CKD. CTA was also used to detect the sensitivity of biomarkers of diabetic nephropathy [17], to estimate the cardiovascular risk in the general population [18] and to determine the cost-effectiveness of CKD mass screening [19].

Studies that investigated the predictors of the annual change in GFR adopted other analytical strategies or were carried out in patients without CKD [20] or in selected patient groups [21, 22], with the exception of a Spanish study conducted in a small sample of patients with advanced CKD [23].

In the present study, CTA identified proteinuria, age, diabetes and serum phosphate levels as the variables that best discriminated patient subgroups. The presence of proteinuria was the first watershed. Patients with proteinuria showed a higher mean annual decrease in eGFR than those without proteinuria (−2.35 mL/min/1.73 m^2 versus −0.8 mL/min/1.73 m^2).

It has been hypothesized that the presence of proteinuria is causally linked to progression of renal damage [20, 21, 24–27]. However, most of these studies were performed in subjects without an important reduction in GFR. Hence, our data confirm the important role of proteinuria in predicting the rate of progression and extend it to patients with CKD.

The CTA divided patients with proteinuria into two further groups: those with a baseline eGFR of ≤33 mL/min (a subset who could be roughly classified as CKD stages 4–5) and those with a baseline eGFR exceeding 33 mL/min (a subset who could be roughly classified as CKD stage 3) and the rate of declining renal function was higher in patients with an eGFR of >33 mL/min/1.73 m^2. This finding indicates that the CKD stage is not *per se* a proof of rapid progression and that it cannot be used alone as the criterion for referral and to schedule follow-up visits. Recently published Kidney Disease: Improving Global Outcomes Guidelines [28] suggest new criteria for referral based on cause of CKD, level of GFR and level of albuminuria. Relying only on the CKD stage for referral to nephrologists in our population would have been misleading, particularly for patients with proteinuria, since a consistent number of fast progressors would have been overlooked.

Among patients with proteinuria and an eGFR of ≤33 mL/min/1.73 m^2, those with serum phosphate levels >4.3 mg/dL showed a >2-fold mean annual eGFR decline compared with patients with a serum phosphate lower than 4.3 mg/dL.

Recently, our group [29] suggested that hyperphosphataemia predicts a rapid deterioration in residual renal function and poor prognosis in CKD patients and Voormolen *et al.* [30] showed that high plasma phosphate is an independent risk factor for a more rapid decline in renal function and a higher mortality during the pre-dialysis phase. Zoccali *et al.* [31] reported that phosphate is an independent risk factor for renal disease progression and that a high phosphate burden may appreciably limit or even blunt the renoprotective effect of ACE inhibitor therapy in patients with proteinuric chronic nephropathies. Serum phosphate was identified as one of a few baseline predictors of renal outcomes also in the AASK study [32]. Finally, in the model of Tangri *et al.* [33], the introduction of serum phosphate levels significantly improved the predictive power of the model.

Although proteinuria has a major role in the CKD progression, in the absence of proteinuria other factors come into play.

Our results indicate that the main factor associated with a differential change in GFR among patients without proteinuria is age. Specifically, CTA sets a cut-off of 67 years below which the mean annual GFR decline is −1.7 mL/min/1.73 m^2, a value certainly above the threshold for 'normal' decline. On the contrary, in patients older than 67 years the GFR decline was −0.5 mL/min/year. Hence, our data confirm that the rate of CKD progression is lower with increasing age, as reported by Van Pottelbergh *et al.* [34] and O'Hare *et al.* [35].

In the group younger than 67 years, the model identified two further subgroups according to the presence or the absence of diabetes. Diabetic patients showed a higher mean

Table 2. Demographic, clinical characteristics and laboratory tests of the seven CTA groups and pairwise comparisons between groups

	CTA group[a]														*F*-test or χ^2 test, *P*
	4		7		8		9		10		11		12		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Male gender	170	73.9%	259	68.5%	73	48.0%	171	64.8%	61	67.8%	0	0.0%	741	100.0%	<0.001
Diabetes	104	45.2%	141	37.3%	67	44.1%	0	0.0%	90	100.0%	118	28.8%	219	29.6%	<0.001
CVD	153	67.1%	284	75.1%	106	69.7%	111	42.2%	70	78.7%	325	79.7%	598	81.0%	<0.001
Smoking	29	20.6%	40	15.7%	22	30.1%	7	5.1%	3	5.7%	6	2.3%	40	6.8%	<0.001
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age, years	63.82	14.43	70.26	13.04	65.74	13.87	54.91	11.67	61.09	6.10	78.56	6.04	78.18	5.82	<0.001
BMI, kg/m^2	27.29	4.78	27.35	4.72	26.77	5.10	26.32	4.51	29.57	5.92	26.59	4.82	26.36	3.68	<0.001
Duration of follow-up, years	4.05	1.34	3.48	1.43	2.58	1.34	3.87	1.45	3.94	1.82	3.69	1.48	3.70	1.47	<0.001
Serum creatinine, mg/dL	1.56	0.39	2.65	0.75	3.20	1.04	2.41	1.19	2.33	0.90	2.15	0.79	2.39	0.85	<0.001
CKD-EPI eGFR, mL/min/1.73 m^2	46.66	13.30	23.22	6.30	18.91	6.79	33.99	16.60	31.89	14.38	24.48	8.96	28.94	10.86	<0.001
Uricaemia, mg/dL	6.19	1.64	6.49	1.84	6.37	1.80	6.26	1.64	6.36	1.61	6.37	1.84	6.48	1.84	0.301
PTH, pg/mL	94.67	73.22	187.28	144.55	219.78	176.33	153.43	143.07	164.77	150.70	185.08	161.43	156.94	117.97	<0.001
Glycaemia, mg/dL	116.62	44.90	112.50	44.28	111.72	41.04	91.65	18.54	145.84	65.15	106.86	41.16	105.03	33.08	<0.001
Hb, gm/dL	13.10	2.82	12.24	1.69	11.63	1.36	13.03	1.92	12.44	1.83	11.96	6.06	12.58	1.70	<0.001
Total cholesterol, mg/dL	202.85	53.42	186.28	43.10	183.68	46.50	193.41	41.13	187.46	48.36	205.11	44.58	181.39	39.37	<0.001
Triglycerides, mg/dL	160.33	85.69	157.79	90.61	147.51	64.45	145.78	76.83	191.62	112.24	151.49	85.54	140.61	76.54	<0.001
HDL cholesterol, mg/dL	52.54	16.25	48.65	15.76	49.26	14.89	51.75	15.57	45.36	12.31	55.81	15.55	47.82	13.04	<0.001
LDL cholesterol, mg/dL	119.63	46.58	107.32	36.62	104.89	41.43	115.00	34.53	112.09	42.48	119.47	41.08	107.70	34.96	<0.001
Post hoc tests															
CTA group															
	4	7	8	9	10	11	12								
	(A)	(B)	(C)	(D)	(E)	(F)	(G)								
Age, years	D	A C D E	D E		D	A B C D E	A B C D E								
BMI, kg/m^2		G			A B C D F G										
Duration of follow-up (years)	BCG	C		BC	C	C	C								
Serum creatinine, mg/dL		A D E F G	A B D E F G	A F	A	A	A F								
CKD-EPI eGFR, mL/min/1.73 m^2	B C D E F G	C		B C F G	B C F	C	B C F								
Uricaemia, mg/dL															
PTH, pg/mL		A	A D G	A		A	A								
Glycaemia, mg/dL	D G	D	D		A B C D F G	D	D								
Hb, gm/dL	B C F			B C F			C F								
Total cholesterol, mg/dL	B C G			G		B C D E G									
Triglycerides, mg/dL		G			B C D F G										
HDL cholesterol, mg/dL	E G					B C E G									
LDL cholesterol, mg/dL	B C G					B C G									

CTA, classification tree analysis; BMI, body mass index; Hb, haemoglobin; HDL, high-density lipoprotein.

[a]Node 4: proteinuria and eGFR>33 mL/min/1.73 m^2; Node 7: proteinuria, eGFR≤33 mL/min/1.73 m^2 and serum phosphorus ≤4.3 mg/dL; Node 8: proteinuria, eGFR ≤33 mL/min/1.73 m^2 and serum phosphorus >4.3 mg/dL; Node 9: no proteinuria, age ≤67 years, no diabetes; Node 10: no proteinuria, age≤67 years, diabetes; Node 11: no proteinuria, age >67 years, female; Node 12: non-proteinuria, age >67 years, male. Note: results are based on two-sided tests assuming equal variances with a significance level of 0.05. For each significant pair, the key of the smaller category appears under the category with larger mean.

decline in GFR (−2.97 mL/min/1.73 m^2), while non-diabetic patients had a mean GFR decline of −1.3 mL/min/1.73 m^2.

This result is in line with other reports suggesting that diabetes may induce renal damage also when the proteinuria is absent [36–39].

Finally, in the large group of older subjects (>67 years), a differential GFR decline was observed in males compared with females. Male patients showed a modest decrease of GFR (−0.8 ± 3.8 mL/min/1.73 m^2), while the female group showed on average no eGFR decline but a large variability (0.05 ± 7 mL/min/1.73 m^2), suggesting a large heterogeneity in the trajectories of change in renal function over time. In previous papers, it has been reported that men with CKD progress at a higher rate than women [40]. It was speculated that gender-specific differences in glomerular structure, haemodynamic condition and sex hormones play a role in the CKD progression. Although our data do not allow investigation of this issue in more detail, they indicate that the progression rate is very low in elderly females compared with males without proteinuria.

Several limitations of the present study should be noted. First, our study population consisted of nephrology-referred CKD patients; therefore, the generalizability of our findings to non-referred CKD patients remains to be determined. In fact, the disease progression observed in the study patients does not reflect the natural course of the disease, but might be affected by the ongoing treatment during the follow-up.

Secondly, patients extracted from the PIRP registry were those with at least four serum creatinine measurements in 1 year. Subjects with kidney dysfunction who may be at risk of progression yet did not have four serum creatinine measurements would not be included. Thus, the study sample includes patients monitored more frequently, which may not be representative of the population of patients being followed up by the nephrologists of the region. This limitation is partially mitigated by our finding that the study population had a similar proportion of females and of patients with diabetes compared with the rest of patients enlisted in the registry, was only 2 years younger and had mean creatinine levels modestly higher (+0.25 mg/dL) at baseline.

Notwithstanding these caveats, our results suggest that it is possible to rely on a small number of variables that are typically accessible in routine clinical practice to stratify patients with a different annual CKD progression rate. Future perspectives include the examination of the effect of CTA-based stratification on process and clinical outcomes in an independent population. Should a benefit of patient stratification be proved, it might be used to guide decisions about treatments to slow progression of kidney disease, prevent its complications and to begin planning for dialysis and transplantation. In addition, patient stratification can help redesign the CKD care service models: 'slow progressors' could be mainly treated by primary care physicians with the supervision of nephrologists, whereas 'fast progressors' (including patients with proteinuria, high levels of serum phosphates or diabetic patients) should be tightly monitored and treated by nephrologists, with an ultimate advantage in terms of an appropriate and efficient resource allocation.

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CONFLICT OF INTEREST STATEMENT

None declared.

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APPENDIX

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