Evolution and outcome of patients with chronic kidney disease in primary care

Evolución y desenlace de pacientes con enfermedad renal crónica en atención primaria

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Abstract

Introduction: Most chronic kidney disease patients are diagnosed and treated in primary care clinics.
Objective: To determine the course of CKD in primary care.
Methods: A prospective cross-sectional study was conducted in 32 primary care practices 1741 people with stage 3 CKD were recruited.
Results: 5-year remission was more likely in the group with remission at baseline and year 1 (OR 23.6, 95% CI 16.5-33.9, p < 0.001).
Conclusions: in a primary care setting, the most common outcome associated with stage 3 CKD over five years was stable renal function.
Keywords: chronic kidney disease, primary care, renal function, comorbidities source: DeCS
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Resumen
Introducción: la mayoría de las personas con enfermedad renal crónica son diagnosticadas y tratadas en clínicas de atención primaria.
Objetivo:Determinarel curso de la ERC en la atención primaria
Método: Se realizó un estudio trasversal prospectivo en 32 prácticas de atención primaria 1741 personas con ERC en etapa 3 fueron reclutadas.
Resultados: La remisión a los 5 años fue más probable en el grupo con remisión tanto al inicio como al año 1 (OR 23,6, IC 95% 16,5-33,9, p < 0,001).
Conclusiones: en un entorno de atención primaria, que el resultado más común asociado con la ERC en estadio 3 durante 5 años fue la función renal estable.
Palabras clave: enfermedad renal crónica, atención pimaria,función renal, comorbilidades.fuente:DeCS

Introduction

In Ecuador and many other countries, most people with chronic kidney disease (CKD) are diagnosed and treated in primary care centers without ever being referred to a nephrologist. In contrast, the most detailed studies investigating

the risks associated with CKD have been led by nephrologists, resulting in a predominantly secondary care perspective. Consequently, guidelines based on these studies emphasize the risk of end-stage renal disease (ESRD) and the need for timely referral to facilitate preparation for renal replacement therapy[1]. In addition, landmark epidemiological studies have highlighted the importance of diagnosing CKD because the defining abnormalities (reduced glomerular filtration rate and albuminuria) are powerful independent risk factors for multiple adverse outcomes, including progression of CKD, acute kidney injury (AKI), excess cardiovascular events (CVE) and increased mortality[2]. However, the prognosis associated with CKD is extremely heterogeneous, and the risk of adverse outcomes varies widely depending on the population studied. For example, population-based studies reported that most people with CKD are at low risk of developing CKD, whereas studies of people with known CKD managed in secondary care report that CKD is a common outcome[3].

Understandably, many previous studies have focused on the risks associated with CKD. However, it is arguably just as important to study positive outcomes as stable CKD or CKD remission so those at low risk of adverse outcomes can avoid unnecessary interventions and referrals to nephrology clinics[4]. Interestingly, there is currently no consensus on when CKD should be considered no longer present (in remission); therefore, there is a lack of readily comparable data to indicate how often remission occurs or the factors contributing to it[5].

Most people with CKD in primary care are elderly, and albuminuria is present in only a minority[6], suggesting that this population is at low risk of progression to end-stage renal disease (ESRD). Therefore, in this prospective cohort study, we sought to detail the natural history of CKD in primary care to better inform the appropriate emphasis for future guidance on caring for persons with CKD in a primary care setting.

Method

A prospective cross-sectional study was conducted in 32 primary care practices in the city of Ambato; 1741 people with stage 3 CKD were recruited individually between 2016 and 2020 and studied prospectively. In total, 8280 people were invited from the registers of people with stage 3 CKD, 1822 attended baseline visits and 1741 were eligible to participate. Participants were >18 years of age and had at least two estimated glomerular filtration rate (eGFR) results (derived from the Modification of Diet in Renal Disease [MDRD] study equation) of 30-59 ml/min/1.73 m^2, more than 90 days apart, were eligible[7]. Individuals considered to have a life expectancy of less than one year, could not attend study visits or had a solid organ transplant were excluded. This study was approved by the Universidad Regional Autónoma de Los Andes (UNIANDES).

Visits were performed at baseline and repeated in the 1st and 5th year. Before each visit, participants completed a background questionnaire covering demographic variables and social, medical, and medication history. Questionnaires were reviewed at study visits and clarified as needed. Weight, height, and waist and hip circumference were measured. In addition, three blood pressure measurements differed by <10% after at least 5 minutes of rest. Participants were asked to refrain from eating meat for 12 h before the study visits to avoid confounding the serum creatinine assay. Blood and urine samples were analyzed at a single clinical laboratory for standard hematologic and biochemical variables. eGFR was estimated using the Chronic Kidney Disease Epidemiologic Collaboration-Epidemiologic (CKD-EPI) equation in the primary analysis[8], with additional sensitivity performed using the MDRD equation. The average urine albumin-to-creatinine ratio (PAC) of three consecutive morning samples was used for the analysis.

The studyapplied the Kidney Disease Improving Global Guidelines (KDIGO) definitions of kidney disease for CKD definition, CKD staging, and CKD progression[7]. CKD progression was defined as a 25% decrease in GFR, a worsening GFR category, or an increase in the albuminuria category. The pre-specified endpoint of the study design (development of CKD or doubling of serum creatinine) was not used due to a very small number of events observed during the year five follow-up. The KDIGO definition was used as an internationally agreed standard of CKD progression most frequently observed in the

study population. CKD remission was defined as the presence of both eGFR >60 ml/min/1.73 m^2 and CAP <3 mg/mmol at any study visit in an individual who had previously met KDIGO diagnostic criteria for CKD.

The database and statistical processing of the data were performed and analyzed in the SPSS 26 statistical program (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for the results collection, presentation and interpretation. The results were analyzed using binomial logistic regression models. Variables significantly associated with outcomes in the univariate analysis were then aggregated into groups according to biological and clinical relevance. The final models included all variables significantly associated with outcomes in previous models and gave the best discrimination. For each model, predicted probabilities were used to draw receiver operating characteristic (ROC) curves, and the area under the ROC curve (AUROC) was used to compare models. Survival analysis was performed using Cox proportional hazards models.

Results

Data on renal outcomes at five years were obtained from 1484 participants (85.2 %). Two hundred forty-seven of 1741 (14.2 %) died before their year five visit, representing an age-standardized annual mortality rate of 4.2 % in men and 2.2 % in women. Four participants (0.2%) reached CKD, and 308 (17.7%) evidenced progression of CKD according to KDIGO criteria. However, 593 participants (34.1 %) had stable CKD and 336 (19.3 %) met CKD remission criteria.

A basic multivariable model including baseline eGFR, sex, PAC, and age as predictors of CKD progression was associated with an AUROC of 0.69 (95 % CI 0.66-0.74). The addition of baseline hemoglobin, bicarbonate, diabetes status, and systolic blood pressure (SBP) produced a model with an AUROC of 0.73 (95 % CI: 0.69-0.76). In this model, baseline age was not statistically significant. The impact of the change at one year on SBP, diastolic blood pressure (DBP) and eGFR was also assessed. The change in eGFR at year 1 was a significant determinant of CKD progression, but the change in SBP and DBP at year 1 did not enter the model.

The cause of death was classified as cardiovascular in 94 cases (38.1 % of 247 deaths), malignancy in 63 (25.5 %), infection in 50 (20.2 %), "other" in 34 (13.8 %) and "no data available" in 6 (2.4 %). Two persons died before year 5 of follow-up but after the development of ESRD. Participants who died tended to be older than other outcome groups and had lower eGFR and higher CAP on average at baseline. Cox proportional hazards models identified age, male sex, baseline eGFR, log PAC, hemoglobin, albumin, and bicarbonate as independent predictors of death. The change in eGFR at year 1 did not enter the model (hazard ratio [HR] = 1.00, p = 0.67).

At baseline, participants who evidenced remission at year 5 had a higher mean eGFR and lower mean CAP than the rest of the study cohort. In addition, participants with remission were younger and evidenced a higher proportion of females (Table 1). A basic multivariable model, including age, sex, eGFR, and log PAC as independent variables, was associated with an AUROC of 0.85 (95 % CI 0.82-0.87) (Table 1). This improved to 0.86 (95 % CI: 0.84-0.88) by adding the change in GFRe observed after one year and baseline hemoglobin. There was no significant difference in weight change between renal outcome groups, nor did weight change enter multivariable models as a predictor of remission.

Table 1. Univariate and multivariate associations of CKD remission at five years.

		MultivariateOdds Ratio (CI 95%)					
variable	UnivariateOdds Ratio (95% CI)	Model 1 (Basic model)	model 2	model 3	model 4	model 5	Model 6 (BestModel)
TFGe	4,92 (3,99-6,06)	4,07 (3,27-5,07)	4,01 (3,21-5,00) *	3,80 (2,99-4,83) *	4,18 (3,34-5,24) *	5,25 (4,09-6,73)	5,10 (3,97-6,55) *
Years	0,50 (0,44-	0,67	0,66	0,70	0,69	0,75	0,76 (0,64-

	0,58)	(0,56-0,79)	(0,56-0,79)	(0,59-0,84) *	(0,57-0,83)	(0,63-0,90) *	0,91) *
female sex	2,30 (1,74-3,04)	1,21 (0,87-1,69)	1,22 (0,87-1,71)	1,44 (0,96-2,18)	1,16 (0,83-1,63)	1,16 (0,83-1,63)	1,34 (0,92-1,94)
PAC Registration	0,60 (0,52-0,68)	0,67 (0,57-0,79) *	0,67 (0,57-0,79)	0,68 (0,57-0,80) *	0,67 (0,57-0,79)	0,69 (0,58-0,81) *	0,69 (0,58-0,81) *
Hemoglobin	1,33 (1,17-1,53) *	-	-	1,22 (1,00-1,49) *	-	-	1,20 (0,99-1,45)
Phosphate	-	-	-	1,04 (0,88-1,23)	-	-	-
Calciumcorrected	1,08 (0,95-1,23)	-	-	0,98 (0,83-1,15)	-	-	-
Bicarbonate	1,32 (1,16-1,51)	-	-	1,17 (0,98-1,38)	-	-	-
Albumin	1,30 (1,14-1,49)	-	-	1,16 (0,97-1,38)	-	-	-
Totalcholesterol	1,23 (1,09-1,39) *	-	-	0,94 (0,80-1,11)	-	-	-
urate	0,52 (0,45-0,61)	-	-	0,96 (0,79-1,17)	-	-	-
Diabetes	0,42 (0,28-0,63)	-	0,79 (0,49-1,28)	-	-	-	-
Previous LCA	0,70 (0,50-0,99)	-	1,12 (0,73-1,70)	-	-	-	-
Currentorformersmoker	0,79 (0,61-1,01)	-	0,97 (0,71-1,32)	-	-	-	-
PAS	0,74 (0,64-0,85) *	-	-	-	0,87 (0,70-1,08)	-	-
PAD	1,18 (1,04-1,35) *	-	-	-	0,95 (0,78-1,16)	-	-
BMI	0,95 (0,83-1,08)	-	-	-	-	-	-
Waistto hip ratio	0,68 (0,60-0,78) *	-	-	-	-	-	-
Year 1 Change in PAS	1,22 (1,07-	-	-	-		1,71	1,70 (1,44-

	1,38) *					(1,45-2,01) *	2,00) *
Year 1 change in PAD	1,11 (0,97-1,26)						
AUROC (95% CI)		0,85 (0,82-0,87)	0,85 (0,82-0,87)	0,85 (0,82-0,87)	0,85 (0,82-0,87)	0,86 (0,84-0,88)	0,86 (0,84-0,88)

Source: statistical analysis, eGFR was calculated using the CKD-EPI equation, and all variables were measured at baseline unless otherwise stated. Odds ratios are expressed per 1 SD increment in the independent variable, p-value < 0.05.

Despite meeting KDIGO diagnostic criteria for stage 3 CKD before study entry, 496 participants (28.5 %) no longer met the criteria for a diagnosis of CKD at the initial study visit. Of this group, 224 (45.2 %) remained in remission at year 5. Remission at five years was more likely in the group with remission at baseline and year 1 (odds ratio relative to those without remission at baseline and year 1 = 23.6, 95% CI 16.5-33.9, $p < 0.001$). Those with remission only at baseline (OR = 5.9, 95 % CI 3.8-9.2, $p < 0.001$) and only at year 1 (OR = 7.1, 95 % CI 4.3-11.8, $p < 0.001$) showed an intermediate probability of remission at 5 years. The group with remission at baseline and year one also showed lower mortality (3.2 %) over five years compared to those with remission only at baseline (5.0 %) and those with remission only at year 1 (5.3 %). Mortality was significantly lower in all groups demonstrating remission at any time than in the group meeting CKD criteria at baseline and year 1 (15.7 %; log-rank test $p < 0.001$).

Discussion

In this population with stage 3 CKD in primary care, most of whom did not meet the criteria for referral to a nephrologist[9], a very low incidence of CKD was observed at five years (0.2 %), and only a minority evidenced progression of KDIGO-defined CKD (17.7 %). As in the population-based studies, the risk of all-cause (14.2 %) and cardiovascular (5.4 %) mortality far exceeded the risk of CKD. Stable CKD (34.1 %) was more common than a progression, and a substantial minority evidenced CKD remission (19.3 %)[10].

The data confirm previous findings in a primary care population that reduced GFR and albuminuria are important independent risk factors for adverse outcomes[11]. In univariable analysis, diabetes was a significant predictor of CKD progression and mortality. After multivariable adjustment, diabetes remained an independent predictor only of CKD progression. However, because diabetes was a predictor of CKD progression, it may have indirectly affected survival through its effect on GFR. Lower hemoglobin independently predicted both CKD progression and all-cause mortality[12]. As reported by investigators in the Chronic Renal Insufficiency Cohort (CRIC) study, lower serum bicarbonate levels were associated with CKD progression[13].

Despite the globally applied criteria for the diagnosis of CKD, there is no consensus on when CKD should be considered to be no longer present (in remission). Therefore, there is a lack of comparable data to indicate how often remission occurs or the contributing factors[14]. The data illustrate the importance of applying the most accurate equation for estimating GFR and avoiding meat before testing (previous studies reported that meat intake could increase serum creatinine by up to 20 µmol/L)[15]. Nevertheless, some participants met diagnostic criteria for CKD at the baseline visit and evidenced remission at 1 and 5 years. The results suggest that changes in medication or hydration status and healing of mild renal damage may have contributed to this remission. Another possibility is that loss of muscle mass with increasing age may result in a decrease in serum creatinine and an increase in eGFR, but this does not appear to have been a contributing factor, as weight change was not associated with remission in this cohort[16]. Improvement in eGFR over time was previously reported in 41 % of participants in a large database study (median

7 ml/min/1.73 m^2 de improvement over 2 years)[17].

Remission at any time was also associated with lower mortality risk. In addition, the results allowed to identify lower age, higher eGFR, and lower CAP as predictors of remission with good discrimination. Thus, these simple variables can be used to identify patients who should be reevaluated for remission or who perhaps should receive a provisional diagnosis rather than a firm diagnosis of CKD. However, it remains to be shown whether those who meet CKD criteria for a short period before improvement carry any excess residual risk[18].

In this analysis, KDIGO definitions were applied for CKD progression. The study protocol specified a definition of ESRD or doubling of serum creatinine as markers of progression, but these endpoints were too infrequently met to be useful for our cohort analysis. However, analysis using the less severe progression of CKD as an endpoint remains relevant because those with more significant declines in eGFR have been shown to have a higher future risk of CKD and all-cause mortality[19,20].

Conclusions

In a primary care setting, the most common outcome associated with stage 3 CKD over five years was stable renal function. In addition, a significant minority of individuals showed remission of CKD. Thus, our data suggest that CKD management in primary care should focus primarily on identifying the minority of people at high risk for adverse outcomes for intervention to slow CKD progression and reduce CVD.

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