

## Association between laboratory and clinical risk factors and progression of the predialytic chronic kidney disease

Associação entre fatores de risco clínicos e laboratoriais e progressão da doença renal crônica pré-dialítica

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### ABSTRACT

**Introduction:** Chronic kidney disease (CKD) is a very common condition that has become a public health issue. Knowing more about risk factors associated with the progression of CKD allows therapeutic interventions that may change the natural course of the disease. **Objective:** To evaluate the impact of clinical and laboratory variables at admission on the outcomes death and need for renal replacement therapy (RRT). **Methods:** A retrospective cohort study comprised of 211 adult patients with stages 3-5 CKD, followed-up for 56.6 ± 34.5 months. **Results:** Mean age of patients was 65.4 ± 15.1 years and 63.5% were > 60 years. The main causes of CKD were hypertensive nephrosclerosis (29%) and diabetic kidney disease (DKD) (17%). Most patients (47.3%) were on stage 4 CKD. The mean annual loss of glomerular filtration rate (GFR) was 0.6 ± 2.5 mL/min/1.73 m<sup>2</sup> (median 0.77 mL/min/1.73 m<sup>2</sup>). After the adjustments for demographic, clinical and laboratory variables, DKD [relative risk (RR) 4.4; 95% confidence interval (CI), 1.47 to 13.2; p = 0.008] was predictive of RRT; age (RR 1.09; 95% CI, 1.04 to 1.15; p < 0.0001) and the non-treatment with angiotensin receptor blocker (ARB) (RR 4.18, 95% CI, 1.34 to 12.9; p = 0.01) were predictors of death. Renal and patient survival rates were 70.9% and 68.6%, respectively. **Conclusion:** In this study, patients with stage 3-5 CKD treated conservatively showed stabilization of renal function and low mortality, which were impacted by DKD, age and to not using ARB, respectively.

**Keywords:** Kidney failure, chronic. Disease progression. Risk factors.

### RESUMO

**Introdução:** A doença renal crônica (DRC) é muito prevalente e representa um importante problema de saúde pública. O maior conhecimento dos fatores de risco relacionados à progressão da DRC permite adotar estratégias terapêuticas que podem alterar o curso natural da doença. **Objetivo:** Avaliar o impacto de variáveis clínicas e laboratoriais à admissão nos desfechos de óbito e início de terapia renal substitutiva (TRS). **Métodos:** Estudo de coorte retrospectiva, composta de 211 pacientes adultos com DRC nos estágios 3-5 tratados, acompanhados por 56,6 ± 34,5 meses. **Resultados:** A idade média dos pacientes foi de 65,4 ± 15,1 anos, sendo 63,5% com > 60 anos. As principais etiologias de DRC foram nefrosclerose hipertensiva (29%) e doença renal diabética (DRD) (17%). A maioria dos pacientes encontrava-se no estágio 4 da DRC (47,3%). A perda média anual de taxa de filtração glomerular (TFG) foi 0,6 ± 2,5 mL/min/1,73 m<sup>2</sup> (mediana 0,7 mL/min/1,73 m<sup>2</sup>). Após os ajustes para as variáveis demográficas, clínicas e laboratoriais, concluiu-se que apresentar DRD [risco relativo (RR) 4,4; intervalo de confiança (IC) 95%, 1,47-13,2; p = 0,008] foi preditor de TRS e a idade (RR 1,09; IC 95%, 1,04-1,15; p < 0,0001) e o não tratamento com bloqueador do receptor da angiotensina (BRA) (RR 4,18; IC 95%, 1,34-12,9; p = 0,01) foram preditores de óbito. A sobrevida renal e a geral dos pacientes foram de 70,9% e 68,6%, respectivamente. **Conclusão:** Neste estudo, os pacientes com DRC nos estágios 3-5 tratados conservadoramente apresentaram estabilização funcional e baixa mortalidade, desfechos associados à DRD, idade e não tratamento com BRA.

**Palavras-chave:** Insuficiência renal crônica. Progressão da doença. Fatores de risco.

## INTRODUCTION

The prevalence of chronic kidney disease (CKD) has increased much in the past decade. In the United States, it is estimated that 13% of the adult population presents with glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m<sup>2</sup>. This prevalence affects 38-44% of the people aged more than 65 years.<sup>1,2</sup> In Brazil, the prevalence of patients on renal replacement therapy (RRT), which was about 42,000 in 2000, overcame 77,000 in the end of 2009; the estimate was 90,000 in 2010.<sup>3,4</sup>

The prevalence rate of the dialytic therapy in 2009 was 405 per million people (pmp), ranging from 165 pmp in the North region to 465 pmp in the Southeast region. Out of the total, 89.6% were on hemodialysis (HD) and 10% were on peritoneal HD, especially automated peritoneal HD.<sup>4</sup> According to previous census, the diagnosis of CKD most commonly found was hypertension, followed by diabetic kidney disease (DKD).<sup>3,4</sup>

From 1983 on, knowing more about physiopathological mechanisms that lead to the loss of nephrons, as well as risk factors related to the progression of CKD, great advances concerning the treatment were observed, which are now the base to slow the progression of the disease.<sup>5</sup>

In this context, factors such as: persistent activity of the base disease, inadequate control of arterial pressure (AP), proteinuria superior to 1 g a day, urinary tract obstruction, reflux and/or urinary infection, painkiller and anti-inflammatory abuse or exposure to other nephrotoxins, congenital or acquired reduction of nephron number, low birth weight, diseases that lead to increased intraglomerular pressure, high-protein diet, diabetes mellitus, pregnancy, dyslipidemia, chronic anemia, smoking and obesity are variables considered as traditional risk factors for the progression of CKD.<sup>6</sup> It has recently been demonstrated that the correction of vitamin D deficiency, hyperuricemia and metabolic acidosis also lead to the decrease of GFR in patients with predialytic CKD.<sup>7-10</sup>

This study aimed to assess the impact of demographic, clinical and laboratory variables that were present at admission and led to the outcomes death or renal replacement therapy (RRT) in patients with stages 3-5 CKD on conservative treatment.

## PATIENTS AND METHODS

Two hundred eleven patients aged more than 18 years with CKD stages 3A, 3B, 4 and 5 were selected, thus originating a retrospective cohort that was followed-up for more than three months, from January 2002

to December 2009 (mean of 56.6 ± 34.5 months) in PREVENRIM – Interdisciplinary Program to Prevent CKD, in *Núcleo Interdisciplinar de Estudos, Pesquisas e Tratamento em Nefrologia* of *Universidade Federal de Juiz de Fora e Fundação – UFJF-IMEPEN*.

This program consists of a interdisciplinary team comprised of a social worker, a nurse, a nephrologist, a nutritionist, and a psychologist, and also prioritizes assistance to patients on CKD stages 3-5. In each appointment, the patient is assisted by the whole team, which enables immediate interventions every time a biopsychosocial problem is identified. At PREVENRIM, patients on CKD stage 3 are followed-up every three months; those on stage 4, every two months; and those on stage 5, monthly.

Demographic and laboratory variables were collected at the time of inclusion in the study: three months.

The considered demographic variables were: age, gender, ethnicity, cause of CKD, number of comorbidities, use of antiproteinuric drugs [angiotensin converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB)], beta blockers, statins, aspirins, erythropoiesis agents, intravenous iron, calcium chelators, vitamin D (colecalciferol or calcitriol) and sodium bicarbonate, besides the total number of used medicines.

The analyzed laboratory variables were proteinuria, creatinine and GFR estimated by the *Chronic Kidney Disease Epidemiology Collaboration* formula (CKD-EPI).<sup>11</sup> The considered clinical variables were AP and body mass index (BMI). The observed outcomes were death, need for RRT and follow-up interruption. This study was approved by the Research Ethics Committee at *Hospital Universitário* of *Universidade Federal de Juiz de Fora – UFJF* (registration n° 203/2011).

## STATISTICAL ANALYSIS

At first, a descriptive analysis of data was conducted, in which data were expressed into mean ± standard deviation, median or percentage, according to the characteristic of the variable. Kolmogorov-Smirnov test was used to analyze normality. Patients were divided into three groups according to the following: continuous follow-up, RRT or death. Afterwards, we performed a univariate analysis with the Chi-squared or ANOVA test. Variables that presented statistical significance were included in a Cox model, having death or RRT as outcomes, depending on the model. Patients were excluded in cases of follow-up interruption. Also, Spearman's correlation between proteinuria, AP and the described events was performed. An

analysis of renal survival and the survival of patients was conducted by the Kaplan-Meier method.  $P < 0.05$  was considered as statistically significant. The software SPSS 15.0 was used.

## RESULTS

Two hundred eleven patients with mean age of  $65.4 \pm 15.1$  years were analyzed; 63.5% were older than 60, and 18% were older than 80. Fifty one percent were females and 63% were white. The main CKD etiologies were hypertensive nephrosclerosis (29%), DKD (17%) and chronic glomerulonephritis (16%). Most

patients were on CKD stage 4 (47.3%), with mean GFR of  $30.6 \pm 14.4$  mL/min/1.73 m<sup>2</sup>. Proteinuria median was 475 mg/24h, mean of systolic AP (SAP) was  $147 \pm 27$  mmHg and diastolic AP (DAP) was  $86 \pm 15.5$  mmHg. Sixty-two percent of the patients used ACEI, 44.8% used ARB and, out of these, 23% were on double blockade. Mean BMI was  $26.3 \pm 4.7$  and 8.5% were smokers (Table 1). A univariate analysis only showed significant data or those that presented statistical trend when comparing the three outcomes. The pre-treatment characteristics associated to higher mortality rates were older age ( $p <$

**Table 1** CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE TOTAL POPULATION IN THE BASE PERIOD

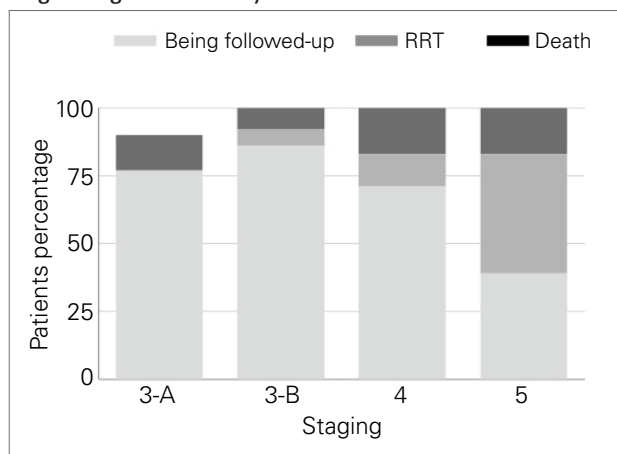
Age in years, mean $\pm$ SD (median)	65.4 $\pm$ 15.1 (67.5)
Elderly ( $\geq 60$ years) %	63.5
Old age ( $\geq 80$ years) %	17.9
Females, %	51
Ethnicity: white, black and brown, %	63/20/17
CKD etiology, %	
Hypertensive Nephrosclerosis	29
Diabetic kidney disease	17
Glomerulonephritis	15.7
Others	38.3
Active smoking, %	8.5
Systolic arterial pressure, mmHg, mean $\pm$ SD	147 $\pm$ 27
Diastolic arterial pressure, mmHg, mean $\pm$ SD	86 $\pm$ 15.5
BMI, mean $\pm$ SD (median, limits)	25.9 $\pm$ 4.7, 25.2 (17.6 – 45.4)
GFR (mL/min/1.73m <sup>2</sup> ) at admission, mean $\pm$ SD	30.6 $\pm$ 14.4
CKD stage at admission, %	
3A	30.2
3B	11.5
4	47.3
5	11
Proteinuria in mg, mean $\pm$ SD (median)	759 $\pm$ 878 (425)
Medications at admission, %	
ACEI	62.3
ARB	44.8
ACEI + ARB	23
Beta blocker	34.4
Statin	51.9
Aspirin	25.5
Vitamin D	9.9
Erythropoiesis stimulating agents	23.6
Sodium bicarbonate	24.1
Calcium carbonate	24.1
Intravenous iron	15.6
Individual use of medicines	5.2
mean $\pm$ SD	
median (variation)	
Number of comorbidities, mean $\pm$ SD, median, limits	2.2 $\pm$ 1.3, 2 (1-10)

SD: standard deviation; CKD: chronic kidney disease; BMI: body mass index; GFR: glomerular filtration rate; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

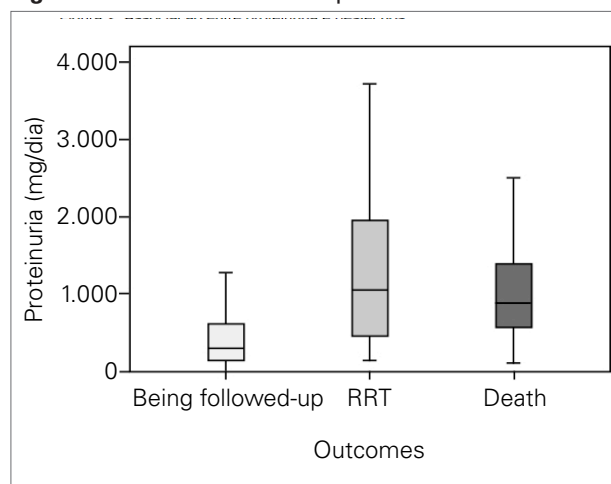
0.0001), CKD stages 4 and 5 ( $p = 0.03$ ), proteinuria ( $p = 0.001$ ) ( $r = 0.311$ ,  $p < 0.0001$ ) (Figure 1) and DKD as etiology for CKD ( $p = 0.01$ ). Patients that died used less ACEI (48%) ( $p = 0.03$ ), beta blockers (17%) ( $p = 0.04$ ) and statin (31%) ( $p = 0.000$ ). No patient among those who died was on vitamin D at

admission ( $p = 0.007$ ). The variables associated with the need for RRT were: age ( $p = 0.000$ ), stages 4 and 5 ( $p = 0.03$ ), DKD ( $p = 0.01$ ) and proteinuria ( $p = 0.001$ ) (Figure 2). Patients with this outcome used less ACEI ( $p = 0.03$ ), ARB ( $p = 0.002$ ), statin ( $p = 0.000$ ) and vitamin D ( $p = 0.007$ ) (Table 2). Figure 3 shows

**Figure 1.** Patients' outcomes from staging in the beginning of the study.



**Figure 2.** Association between proteinuria and outcomes.

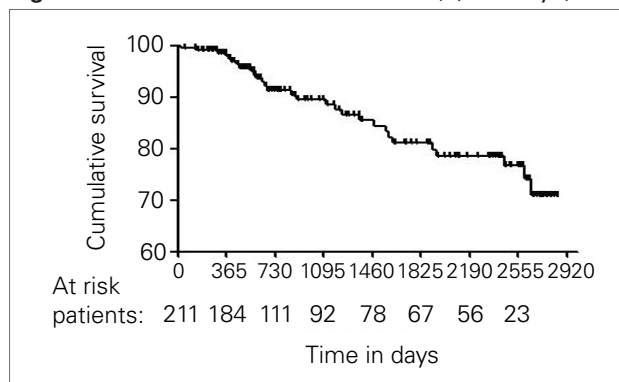


**Table 2** COMPARISON OF CLINICAL AND LABORATORY CHARACTERISTICS IN RELATION TO OUTCOMES

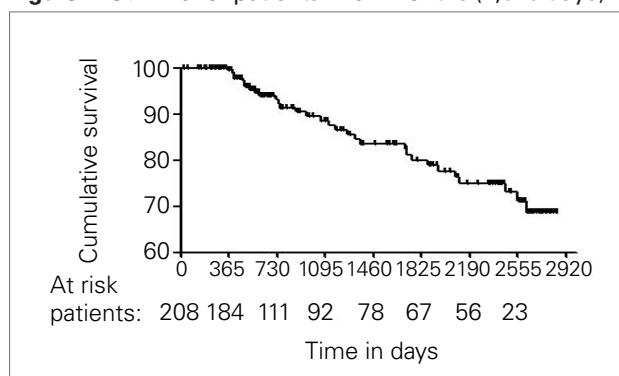
Variables	Being followed-up (n = 149)	RRT (n = 33)	Death (n = 29)	p-value
Age in years, mean $\pm$ SD	63.5 $\pm$ 14.9	64 $\pm$ 14.5	78 $\pm$ 7.5	< 0.0001
Elderly ( $\geq 60$ years); n, %	88 (65.7)	17 (12.7)	29 (21.6)	< 0.0001
Old age ( $\geq 80$ years), n, %	17 (47)	5 (14)	14 (14)	< 0.0001
CKD etiology, n, %				0.013
Hypertensive nephrosclerosis	49 (33)	9 (27)	11 (38)	
Diabetic kidney disease	17 (11)	11 (33)	3 (10)	
Glomerulonephritis	19 (13)	7 (21)	5 (17)	
Others	64 (43)	6 (18)	10 (34)	
CKD stage at admission, %				0.032
3A	24 (16)	0	3 (10)	
3B	45 (30)	3 (9)	4 (14)	
4	60 (40)	10 (30)	14 (48)	
5	7 (5)	8 (24)	3 (10)	
Proteinuria in mg, mean $\pm$ SD	560 $\pm$ 752	1179 $\pm$ 943	1027 $\pm$ 769	0.001
Medications at admission, %				
ACEI	91 (61)	18 (55)	14 (48)	0.032
ARB	75 (50)	7 (21)	10 (34)	0.021
Beta blocker	50 (34)	10 (30)	5 (17)	0.042
Statin	94 (63)	4 (12)	9 (31)	< 0.0001
Aspirin	42 (28)	1 (3)	8 (28)	0.001
Vitamin D	20 (13)	1 (3)	0	0.007
Erythropoiesis stimulating agents	39 (26)	6 (18)	3 (10)	0.056
Sodium bicarbonate	40 (27)	5 (15)	4 (14)	0.061
Intravenous iron	6 (4)	4 (12)	0	0.062

SD: standard deviation; CKD: chronic kidney disease; BMI: body mass index; GFR: glomerular filtration rate; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

**Figure 3.** Renal survival in 94 months (2,820 days).



**Figure 4.** Survival of patients in 94 months (2,820 days).



**Table 3** ANALYSIS OF COX MULTIVARIATE REGRESSION, WITH THE OUTCOMES OF RRT (MODEL 1) AND DEATH

Outcome	Relative Risk	95% CI Inferior limit – Superior limit	p-value
<b>RRT</b>			
CKD-EPI-1	0.967	0.924 – 1.013	0.154
Age	0.979	0.944 – 1.014	0.236
Proteinuria	1.248	0.453 – 3.430	0.668
ACEI-1	0.987	0.247 – 3.942	0.986
ARB-1	0.973	0.301 – 3.143	0.963
DKD	4.417	1.473 – 13.242	0.008
<b>Death</b>			
CKD-EPI-1	0.998	0.973 – 1.024	0.890
Age	1.098	1.046 – 1.152	< 0.0001
Proteinuria	0.735	0.233 – 2.322	0.600
ACEI-1	1.539	0.516 – 4.594	0.439
ARB-1	4.180	1.345 – 12.990	0.013
DKD	1.248	0.337 – 4.628	0.740

CKD-EPI-1- reference (stage 1); Age: continuous variable; Proteinuria: continuous variable; ACEI and ARB- reference: non use; DKD: presence of diabetic kidney disease.

renal survival in the period, and Figure 4 shows survival of patients. The mean annual loss of GFR was  $0.6 \pm 2.5$  mL/min/1.73 m<sup>2</sup>, with median of 0.77 mL/min/1.73 m<sup>2</sup>.

The evaluation of the incidence death rate and need for RRT shows the following numbers: 29.16/1000 patients/year and 33.18/1000 patients/year, respectively.

In Table 3, it is possible to observe that using the variables that were significant at the univariate analysis in the Cox regression model, the variable DKD as etiology of CKD [relative risk (RR) 4.4; confidence interval (CI) 96%, 1.47–13.2; p = 0.008] was the only one that predicted RRT; When the variable of the outcome was death, predictive variables were: age (RR 1.09; 95% CI, 1.04–1.15; p < 0.01) and the non-treatment with ARB (RR 4.18; 95% CI, 1.34–12.9; p = 0.01).

### DISCUSSION

In this study, it was important to identify demographic, clinical and laboratory variables that were present in the beginning of the study and were associated to the outcomes of RRT and death, thus leading to interventions that could change the speed of renal function loss and decrease chances of early mortality due to CKD. A univariate analysis showed that, except for AP levels, the outcomes need for RRT or death were associated with GFR, age, proteinuria, DKD, which are classic determining factors for these outcomes. It was also observed that variables represented by replacing vitamin D (active or not) and replacing sodium bicarbonate were associated with a favorable impact on the course of the disease.

The sample consisted mostly of elderly participants (63.5%), which is in accordance with other studies.<sup>12-14</sup> The prevalent CKD etiology was hypertensive nephrosclerosis (29%), followed by DKD (17%) and chronic glomerulonephritis (16%), which are related to the main causes of CKD in patients who underwent HD in Brazil.<sup>3</sup> Sesso *et al.* and Fernandes *et al.* showed that most patients who start on RRT in our country is referred to nephrology services very late, and most are on stage 4 (47.3%), which contrasts with data in international literature, in which most patients are on stage 3.<sup>3-15</sup>

Besides the expected contribution of age and CKD staging, the correlation of proteinuria with the progression of the renal disease, even if eased by the



renoprotection by ACEI and ARB, is demonstrated in many studies.<sup>16-18</sup> This phenomenon is clearly observed in patients with type II DM, in which ¼ of the patients presents with renal compromise after ten years of disease.<sup>19</sup>

Proteinuria was also associated with higher mortality rates, as published by other authors who demonstrated this is a risk factor that is not connected to cardiovascular mortality.<sup>20,21</sup>

On the other hand, the relation between the use of statins and lower mortality rates, as well as the slower progression to renal function failure with the need for RRT, is controversial. The 4S study<sup>22</sup> showed an important benefit, which slows the progression, while ALLHAT<sup>23</sup> could not show any differences. The relation between using statins and lower cardiovascular mortality rates in the general population is documented in literature,<sup>24</sup> as well as the use of beta blockers.<sup>25</sup>

The protective effect observed by the use of vitamin D in this study does not allow us to establish a definitive association with favorable outcomes, once the evolution of a dynamic retrospective cohort that started in 2002 was analyzed, time when the use of vitamin D was not really common. Patients took part in the study in different moments, and the use of vitamin D became more frequent with time. Considering these facts, it is interesting to observe the results are in accordance with prior studies, which clearly showed the important benefits of vitamin D for CKD.<sup>8,26</sup>

In the beginning of the study, the observation that SAP and DAP were inadequate and were not associated to the outcomes represented by the need for RRT and death deserves some attention, even though it was not the only observation. The fact that pressure levels were higher than recommended in the base period of the study does not necessarily mean that they stayed this way during follow-up.

Also, this study included patients from different ethnicities, which is common in Brazil, and this may have made it more difficult to observe the correlation between ethnicity and outcomes. The non-association of pressure levels at admission with the progression of CKD was also noticed in an observational study with 1,094 African-American patients,<sup>27</sup> and in patients with adult polycystic kidney disease.<sup>28</sup>

More recently, in a meta-analysis performed by Upadhyay *et al.*, the authors concluded there was no clinical advantage in keeping pressure levels lower than 130 x 80 mmHg, in comparison to levels lower

than 140 x 90 mmHg, except for the subpopulation comprised of patients with CKD and proteinuria between 300 and 1,000 g/24h, since they presented better clinical course of the disease.<sup>29</sup>

On one hand, in a Cox regression model that considers CKD staging as the main variable, it was possible to observe that only DKD presented itself as a risk factor for RRT; on the other hand, risk factors for death after adjusting the model were CKD staging, age and not using ARB.

Thus, we noticed that only the immutable variables at admission, like age and etiology, were determining factors for the worst outcomes; meanwhile, those variables that were likely to change by means of clinical treatment were not determining. The mean annual loss of GFR was  $0.6 \pm 2.5$  mL/min/1.73 m<sup>2</sup>, with median of 0.775 mL/min/1.73 m<sup>2</sup>, which is much lower than what is established in the guidelines about CKD (NICE),<sup>30</sup> and renal survival was 70.9%. Survival of patients was 68.6%, which confirms the positive impact of the intervention during follow-up. One limiting factor of this study is the possibility to analyze patients after a three-month follow-up, and only those who are referred to the nephrologist. This creates selection bias, which partly explains the good results presented.

The complexity of CKD requires that the patient be ideally assisted by an interdisciplinary team. Studies conducted with children<sup>31</sup> and adults<sup>32</sup>, in comparison to the conventional model focused on the nephrologist, show the superiority of managing CKD with an interdisciplinary team in relation to clinical outcomes and reaching the parameters proposed by the Kidney/Disease Outcomes Quality Initiative (K/DOQI) at the beginning of dialysis.

Interdisciplinary care makes sense, and its basic premise is that patients with complex diseases, such as CKD, need to be treated by different health professionals, thus leading to the identification of medical, psychosocial and functional issues.

In Brazil, as observed in other countries, the experience with the interdisciplinary care for patients with CKD is still very limited. PREVENRIM is an interdisciplinary program for the secondary prevention of CKD. It is not restricted to monitoring renal function, but is also a holistic approach to CKD, reaching the different biopsychosocial aspects of the condition. The assistance model is circular, that is, patients are assisted by all health professionals at the same appointment, whenever necessary. In each visit, all professionals reinforce the main points regarding their field of activity with the objective to optimize the treatment.<sup>33</sup>

In this study, it was not possible to evaluate the low renal function loss in mechanical terms (and the consequent low need for RRT) and the low mortality rate. In the current study, it will be analyzed if the time of maintenance of clinical variables in therapy limits proposed in different guidelines is the main determining factor for the evolution of CKD.

Finally, this outcome analysis suggests that the exposure to a structured nephrology care for conservatively treated patients with CKD was associated to the functional stabilization and low mortality rates, which are outcomes impacted by the occurrence of CKD, age and not using ARB, respectively.

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