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Article

Progression of chronic kidney disease in non-dialysis patients: a retrospective cohort

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Evidence on factors associated with the progression of chronic kidney disease (CKD) is still under construction. The present study aimed to evaluate sociodemographic, clinical, and drug use factors associated with the progression of CKD. A retrospective cohort study was conducted with 193 patients with CKD stages 3A to 5- non-dialysis followed for three years in a Brazilian city. The outcome was the evolution to renal replacement therapy (RRT) or death. A total of 52.3 % (n = 101) were men and 83.4 % (n = 161) elderly. The median age was 72.0 years, and 22.3 % (n = 44) progressed to RRT or death, and the three-year mortality rate was 20.2 %. Participants exposed to angiotensin converting enzyme inhibitors or angiotensin II receptor blockers had a lower risk of progressing to the outcome (hazard ratio (HR) 0.25; p = 0.003) and higher survival (p = 0.022) when compared to those not exposed to these drugs. Age (HR 1.06;) and use of omeprazole (HR 6.25; CI; p <0.01) and hydrochlorothiazide (HR 2.80; p = 0.028) increased the risks of RRT or death. The results highlight the importance of rational management of pharmacotherapy for patients with CKD.

Keywords: Chronic kidney disease. Disease progression. Drug utilization. Drug therapy. Nephrology.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health concern due to the increase in its prevalence, as a consequence of population aging and associated diseases, such as diabetes mellitus (DM) and systemic arterial hypertension (SAH) (Eckardt *et al.,* 2013; Mariani *et al.,* 2016). CKD affects about 10 % of the world population and more than a third of the elderly (Stengel *et al.,* 2011; Stengel *et al.,* 2014). In Brazil, it is estimated that 3 to 6 million Brazilians have some degree of kidney disease (Marinho *et al.,* 2017).

Furthermore, the prevalence estimate of patients in dialysis is 640 patients per million of the population and the incidence is 204 patients with end-stage renal disease on maintenance dialysis per million of the population. In 2018, a total of 133,464 patients were undergoing dialysis treatment in the country (Sociedade brasileira de nefrologia, 2018).

With the increase in the incidence and prevalence of this disease, the need for renal replacement therapy (RRT) also increases, in addition to the increased risk of

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mortality and the need for specialized healthcare (Murphy *et al.,* 2016).

Several factors have been related to the spread of CKD, such as elevated blood pressure, uncontrolled DM, dyslipidemia, obesity, smoking, proteinuria, and use of nephrotoxic substances (Schaefer, Wühl, 2012; Bochud, 2015; Webster *et al.,* 2017). The clinical guidelines for conservative treatment of CKD determine that the therapeutic approach aims to reduce its progression (NKF, 2013). Among the main clinical practices, the use of renin angiotensin aldosterone system blockers, represented by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) have been shown to be effective in reducing the progression of the disease (Lewis *et al.,* 1993). In addition, non-exposure to nephrotoxic drugs and better control of clinical and laboratory parameters of SAH, DM, dyslipidemia, uric acid, and acidosis can have a positive impact in delaying the progression of CKD (Eckardt *et al.,* 2013; Ministério da Saúde, 2014).

The transition to the final stage of kidney disease is a time of high clinical risk with profound effects on mortality, morbidity, quality of life, and use of health resources (Mariani *et al.,* 2016). CKD often advances to the terminal phase and the need for RRT, and in recent years new studies on factors associated with the progression of CKD have emerged (Go *et al.,* 2004; Chiu *et al.,* 2008; Khan *et al.,* 2017). However, evidence on the impact of treatment options on preventing the development of CKD and on patient survival is still under construction, especially within the scope of the Brazilian Public Health System (SUS) where we do not have government data regarding these patients.

Therefore, the aim of this study was to evaluate sociodemographic, clinical, and drug use factors associated with the progression of CKD for the outcome of onset of RRT or death in patients with CKD in stages 3A to 5 non dialytic (ND), under conservative treatment.

METHODS

Study design, population and location:

This is a retrospective cohort with three years of follow-up, including an initial baseline assessment, and follow-up every six months (Figure 1). The study was conducted in Divinópolis in the state of Minas Gerais (MG), Brazil, whose estimated population is 235,977 inhabitants. Patients over 18 years old who received initial care between 2014 and March 2016 or were already being followed up at the Municipal Outpatient Clinic for Nephrology in Divinópolis and had an established diagnosis of CKD stages 3, 4, or 5-ND after three months of evaluation were included in the cohort. Patients with neoplasms or absence of creatinine values were excluded. Patients who attended only at baseline were considered losses.

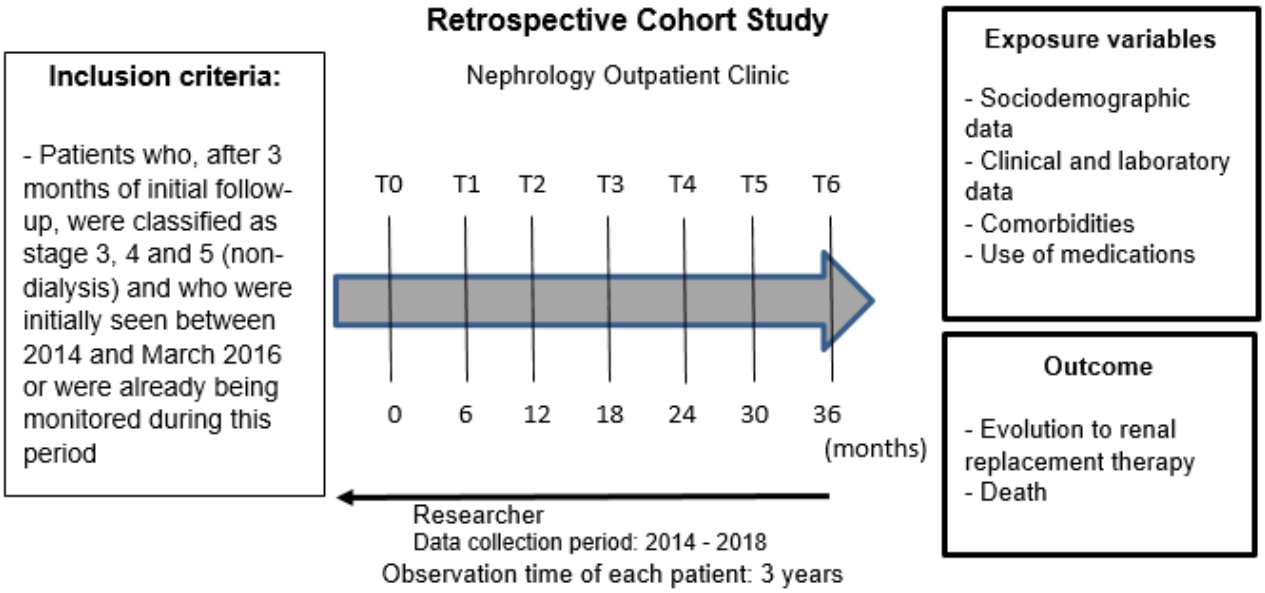

FIGURE 1 - Schematic representation of the stages of construction of the cohort study in patients with CKD in stages 3 to 5-ND in Divinópolis (MG), Brazil.

The Municipal Nephrology Outpatient Clinic is inserted in the Polyclinic of Divinópolis (MG), where patients who need renal care are served. The outpatient clinic follows the recommendations of the guidelines for the care of patients with CKD, which recommends that nephrological assessments in patients with CKD in stages 3A and 3B are semiannual, stage 4 quarterly, and stage 5-ND monthly (Ministério da Saúde, 2014). In each consultation, creatinine tests are requested and the glomerular filtration rate (GFR) is estimated, using the formula proposed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) group (NKF, 2013). Tests indicated in nephrology at the frequency recommended by the clinical guidelines, and tests used to monitor the control of comorbidities such as DM, SAH and anemia are also requested (Ministério da Saúde, 2014).

Data collection, exposure variables and outcome:

Data collection by the researchers took place between December 2017 and March 2018, looking for data retrospectively. A structured instrument developed for this research was used containing sociodemographic information, clinical and family history, clinical parameters, laboratory tests performed at each consultation, and prescribed drugs. The sources of information were the patient's medical record and the Health Information System (SIS) - an online system used by the SUS. The medical record contains information regarding clinical history, management, tests, and prescribed drugs, while the SIS contains sociodemographic data, laboratory tests performed by the SUS, authorization of procedures (such as hemodialysis), hospitalizations, dispensed drugs, and death certificates.

The exposure variables were gender, age at baseline, stage and time of CKD diagnosis, marital status, education, color or race, smoking, comorbidities, control of clinical and laboratory parameters related to CKD, and drug use. A dichotomy was carried out as to whether or not the clinical and laboratory parameters were adequate at baseline according to the goals established by the main guidelines and studies. Control of blood pressure levels was considered as: blood pressure <140/90 mmHg for patients without DM and ≤130/80 mmHg for patients with DM (MS, 2014); glycemic control: fasting glycemia ≤130 mg/dL and glycated hemoglobin (HbA1c) <7 %

(assessed only for patients with DM) (SBD, 2017); lipid control: LDL <100 mg/dL, HDL for women ≥50 mg/dL and for men ≥40 mg/dL, triglycerides <150 mg/dL (Faludi *et al*., 2017); uric acid control: <7.0 mg/dL (NKF, 2013); urea: 20-40 mg/dL; hemoglobin for women 12 to 15.5 g/dL and men 14 to 18 g/dL; calcium 8.8 to 11.0 mg/dL (Abensur, 2011); and phosphorus in stages 3 and 4 of 3.0 - 4.6 mg/dL (NKF, 2013).

For medication, the use of nephroprotective (ACE inhibitors or ARB), and nephrotoxic drugs (non-steroidal anti-inflammatory drugs and omeprazole) were evaluated, in addition to the most prescribed drugs among the participants. Users of these drugs were considered to be patients who had used them for more than six months. The outcome assessed was progression to RRT or death from any cause after initial follow-up within three years.

Statistical analysis:

Comparison analyzes were performed between patients who remained in the cohort and losses, using the Chi-square test to analyze proportions, and the non-parametric Mann-Whitney test to compare medians. A descriptive analysis of the data was subsequently performed according to the patients who evolved or not for the outcome, expressed as median and interquartile range (IQ) for data with abnormal distribution or percentage, according to the characteristic of the variable. To assess normality, the Kolmogorov-Smirnov test was used. A univariate analysis was then performed using the Chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney test for continuous variables with non-normal distribution. The variables that presented p values <0.20 in the univariate analysis and the variables gender and use of omeprazole were included in a Cox Regression model, with the outcome variable RRT or death. Subsequently, those with p values >0.05 and without statistical significance were excluded from the model.

An analysis of overall patient survival was performed using the Kaplan Meier method and a second analysis evaluated survival considering the groups that used or did not use drugs that showed statistical significance in the Cox model. To compare the survival curve between groups, the logrank test was used. P <0.05 and 95 % confidence interval (CI) were considered statistically significant. For the analyzes, STATA 14.1 software was used.

The project was approved by the Ethics Committee of the Federal University of São João Del-Rei - Centro-Oeste dona Lindu Campus (UFSJ-CCO), approval protocol 3.010.366, CAAE: 65858117.3.0000.5545.

RESULTS

Between 2014 and 2016, 406 patients were treated at the Municipal Nephrology Outpatient Clinic. Of these, 217 were diagnosed with CKD in stages 3A to 5-ND. However, 6.4 % (n = 14) were excluded due to previous diagnosis of neoplasms or due to the absence of creatinine tests. Thus, 203 patients were included in this study. The median age was 72 (IQ: 62 to 82) years.

A total of 4.9 % (n = 10) attended only the first consultation, with no future evolution data, and therefore were considered losses. Figure 2 shows the details of the recruitment and follow-up of the participants. In patients who have not progressed, the mean creatinine levels were 1.39 ± 0.16 mg/dL in stage 3A; 1.66 ± 0.28 mg/dL in stage 3B; 2.34 ± 0.45 mg/dL in stage 4, and the mean GFR levels were 50.4 ± 4.0 mL/min/1.73 m² in stage 3A; 36.2 ± 4.6 mL/min/1.73 m² in stage 3B; and 23.6 ± 4.1 mL/min/1.73 m² in stage 4. In patients who progressed the mean creatinine levels were 1.43 ± 0.23 mg/dL in stage 3A; 1.70 ± 0.29 mg/dL in stage 3B; 2.29 ± 0.57 mg/dL in stage 4; 3.34 ± 0.37 mg/dL in stage 5, and the mean GFR levels were 49.4 ± 5.5 mL/min/1.73 m² in stage 3A; 35.2 ± 4.7 mL/min/1.73 m² in stage 3B; 23.1 ± 3.1 mL/min/1.73 m² in stage 4; and 14.0 ± 1.4 mL/min/1.73 m² in stage 5.

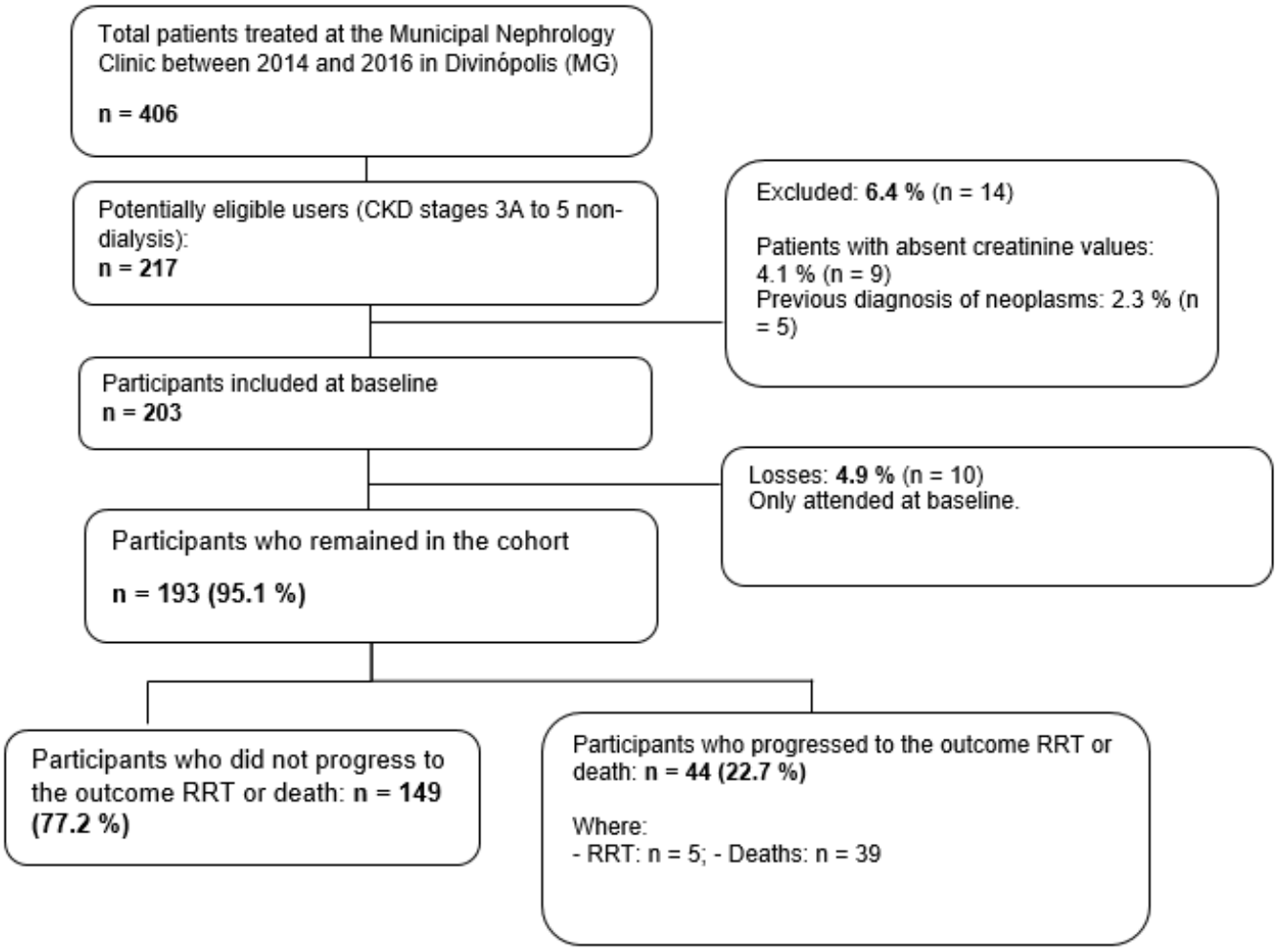

FIGURE 2 - Flowchart of recruitment and follow-up of patients with CKD in stages 3 to 5-ND in Divinópolis (MG), Brazil.

Among the 193 patients in the cohort, 52.3 % (n = 101) were male and 83.4 % (n = 161) elderly (≥ 60 years). There was a higher prevalence of individuals who were married or in a stable relationship (50.3 %), who had studied from one to four years (50.3 %), and of the white race (37.3 %). It is noteworthy that 90.2 % (n = 174) of the participants had SAH and 42.5 % (n = 82) had type 2 DM. Of the participants, 22.3 % (n = 44) progressed to RRT or death. Patients who progressed, despite having significantly shorter CKD diagnosis time (12 months [IQ 4.0-21.0] *vs*. 23 months [IQ 16.5-25.0]; p <0.01) were older when compared to those who did not progress (78.0 years [IQ: 69.5 - 81.5] *vs*. 70.0 years [IQ: 62.0-79.0]; p <0.01). The characteristics of the patients are shown in Table I.

TABLE I - Sociodemographic and clinical characteristics of patients with Chronic Kidney Disease at baseline, attended between 2014 and 2016 at the Municipal Nephrology Outpatient Clinic in Divinópolis (MG), Brazil (n = 193)

Variable	Total (n=193) N (%)	Not progressed (n=149) N (%)	Progressed (n=44) N (%)	*P value*
Gender				
Male	101 (52.3)	81 (54.4)	20 (45.5)	0.229*
Female	92 (47.7)	68 (45.6)	24 (54.5)	
Age (years)	72.0 (62.5-80.0)	70.0 (62.0-79.0)	78.0 (69.5-81.5)	**0.006****
Diagnosis time (months)	21.0 (12.0-24.0)	23.0 (16.5-25.0)	12.0 (4.0-21.0)	**0.001****
Marital status				
Married/Stable Union	97 (50.3)	74 (49.7)	23 (52.3)	
Others	55 (28.5)	38 (25.5)	17 (38.6)	**0.048***
Not registered	41 (21.2)	37 (24.8)	4 (9.1)	
Years of study				
Illiterate	20 (10.4)	16 (10.7)	4 9.1)	
from 1 to 4	97 (50.3)	67 (45.0)	30 (68.2)	0.124*
4 to 8	16 (8.3)	15 (10.1)	1 (2.3)	
Above 8	18 (9.3)	16 (10.7)	2 (4.5)	
Not registered	35 (21.8)	42(23.5)	7 (15.9)	
Color or race				
White	72 (37.3)	55 (36.9)	17 (38.6)	
Mixed	26 (13.5)	18 (12.1)	8 (18.2)	
Black	47 (24.4)	2 (1.3)	1 (2.3)	0.789*
Asian	3 (1.6)	38 (25.5)	9 (20.5)	
Not registered	45 (23.3)	36 (24.2)	9 (20.5)	
Smoking				
No	81 (42.0)	62 (41.6)	19 (43.2)	
Yes	22 (11.4)	20 (13.4)	2 (4.5)	0.430*
Ex-smoker	8 (4.1)	6 (4.0)	2 (4.5)	
Not registered	82 (42.5)	61 (40.9)	21 (47.7)	
Comorbidities				
Hypertension	174 (90.2)	134 (89.9)	40 (90.9)	1.000***
Type 2 Diabetes Mellitus	82 (42.5)	61 (40.9)	21 (47.7)	0.424*
Anemia	50 (25.9)	38 (25.9)	12 (27.3)	0.814*
Dyslipidemia	39 (20.2)	36 (24.2)	3 (6.8)	**0.010*****

TABLE I - Sociodemographic and clinical characteristics of patients with Chronic Kidney Disease at baseline, attended between 2014 and 2016 at the Municipal Nephrology Outpatient Clinic in Divinópolis (MG), Brazil (n = 193)

Variable	Total (n=193) N (%)	Not progressed (n=149) N (%)	Progressed (n=44) N (%)	*P value*
Gouty Arthritis	27 (14.0)	23 (15.4)	4 (9.1)	0.335***
CKD stage				
Stage 3a	65 (33.7)	55 (36.9)	10 (22.7)	
Stage 3b	75 (38.9)	59 (39.6)	16 (36.4)	**0.016***
Stage 4	51 (26.4)	35 (23.5)	16 (36.4)	
Stage 5-ND	2 (1.0)	0 (0.0)	2 (4.5)	
Total patients with inadequate parameters control				
Uncontrolled SBP	87 (45.1)	66 (44.3)	21 (47.7)	0.898*
Uncontrolled DBP	112 (58.0)	84 (56.4)	28 (63.6)	0.692*
Elevated capillary glycemia	27 (14.0)	20 (13.4)	7 (15.9)	0.832*
Elevated HbA1c	30 (15.5)	23 (15.4)	7 (15.9)	0.574*
Elevated LDL	92 (47.7)	33 (22.1)	9 (20.5)	0.715*
Elevated triglycerides	34 (17.6)	26 (17.4)	8 (18.2)	0.703*
Elevated uric acid	76 (39.4)	55 (36.9)	21 (47.7)	0.434*
Elevated urea	152 (78.8)	116 (77.9)	36 (81.8)	**0.045***
Reduced hemoglobin	91 (47.2)	66 (44.3)	25 (56.8)	0.340*
Reduced calcium	12 (6.2)	9 (6.0)	3 (6.8)	0.211*
Elevated phosphorous	5 (2.6)	4 (2.7)	1 (2.3)	0.941*
Elevated potassium	27 (14.0)	19 (12.8)	8 (18.2)	0.469*

Table Legend: * Chi-square test; ** Data with abnormal distribution, expressed as median and interquartile range, non-parametric Mann-Whitney test; *** Fisher's exact test. Legend: HbA1c: glycated hemoglobin; CKD: chronic kidney disease; LDL: low density lipoprotein; HDL: High density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; ND: non-dialytic.

A total of 79.8 % (n = 154) made use of ACE inhibitors or ARB, with the highest use being ARB (n = 128; 66.3 %). The reasons why some patients were not using ACE inhibitors and ARB were: hyperkalemia induced by these drugs, intolerance to drugs, intolerance of pressure levels, and decreased GFR levels after the start of use. ARB, simvastatin, furosemide and acetylsalicylic acid were the most prescribed drugs. There was a significant difference between the use of hydrochlorothiazide (p = 0.020) and insulin (p = 0.038) between the groups that progressed or not to RRT or death (Table II). Among the patients who progressed, 29.5 % (n = 13) used omeprazole and only 2.3 % (n = 1) used non-steroidal anti-inflammatory drugs, with no significant difference in the use of these nephrotoxic drugs compared to the group that did not progress in the univariate analysis.

TABLE II - Use of nephroprotective, nephrotoxic, and other drugs more prevalent in patients with chronic kidney disease, attended between 2014 and 2016 at the Municipal Nephrology Ambulatory, in Divinópolis (MG), Brazil (n = 193)

Variable	Total (n=193)	Not progressed (n=149) N (%)	Progressed (n=44) N (%)	P value
Use of nephroprotective drugs				
ACE inhibitors or ARB	154 (79.8)	121 (81.2)	33 (75.0)	0.366*
Chronic use of nephrotoxic drugs				
Omeprazole	67 (34.7)	54 (36.2)	13 (29.5)	0.412*
NSAID	12 (6.2)	11 (7.4)	1 (2.3)	1.000**
Use of other Drugs				
Acetylsalicylic acid	95 (49.2)	73 (49.0)	22 (50.0)	0.907*
Allopurinol	66 (34.2)	52 (34.9)	14 (31.8)	0.705*
Beta blocker	86 (44.6)	71 (47.7)	15 (34.1)	0.112*
Calcium carbonate	20 (10.4)	16 (10.7)	4 (9.1)	0.665**
Calcium Channel Blocker	54 (28.0)	44 (29.5)	10 (22.7)	0.364*
Clopidogrel	30 (15.5)	24 (16.1)	6 (13.6)	0.691*
Colchicine	17 (8.8)	14 (9.4)	3 (6.8)	0.767**
Ferrous sulphate	23 (11.9)	21 (14.1)	2 (4.5)	0.086*
Furosemide	99 (51.3)	76 (51.0)	23 (52.3)	0.883*
Hydrochlorothiazide	63 (32.6)	55 (36.9)	8 (18.2)	**0.020***
Insulin	53 (27.5)	40 (26.8)	13 (29.5)	**0.038***
Simvastatin	101 (52.3)	79 (53.0)	22 (50.0)	0.725*
Spironolactone	27 (14.0)	21 (14.1)	6 (13.6)	0.939*
Sulfonylurea	18 (9.3)	13 (8.7)	5 (11.4)	0.597*
Vitamin D	33 (17.1)	24 (16.1)	9 (34.1)	0.501*

Legend: NSAID: non-steroidal anti-inflammatory drugs; DM: diabetes mellitus. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker. * Chi-square test; ** Data with abnormal distribution, expressed as median and interquartile range, non-parametric Mann-Whitney test.

Table III represents the Cox regression model using the gender variable and variables that were significant in the univariate analysis. It was observed that age and use of hydrochlorothiazide and omeprazole were predictors of the outcome RRT or death. Omeprazole had a hazard ratio (HR) of 6.25 (CI: 2.32 - 16.78), indicating a risk of progression to RRT or death of approximately six times higher in omeprazole users when compared to non-users. Hydrochlorothiazide however, whose HR was 2.80 (CI: 1.12 - 7.05), indicated a risk of almost three times greater among users of this drug. However, the variable use of ACE inhibitors or ARB represented protection for the outcomes.

TABLE III - Multivariate Cox Regression Analysis, with the outcome variable being the need for RRT, or death.

Exposure variables	Hazard Ratio (HR)	CI 95% (Lower limit – Upper limit)	P value
Gender	0.42	0.17- 1.04	**0.060**
Age	1.06	1.02 – 1.11	**0.009**
ACE inhibitors or ARB	0.25	0.10 – 0.62	**0.003**
Omeprazole	6.25	2.32 – 16.78	**0.001**
Hydrochlorothiazide	2.80	1.12 – 7.05	**0.028**
Insulin	0.62	0.26 – 1.45	0.267

Legend: ACE inhibitors: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CI: confidence Interval.

The 3-year mortality rate was 20.2 % (39/193). Figure 3 shows the patients' survival during the study, estimated by the Kaplain Meier method. Figure 4 shows the participants' survival estimates according to whether or not they used ACE inhibitors or ARB over 500 days. Survival differed significantly (p = 0.022) by the logrank test between groups that were or were not exposed to nephroprotective drugs: patients treated with ACE inhibitors or ARB had better survival compared to those who did not use these drugs at any time (Figure 4).

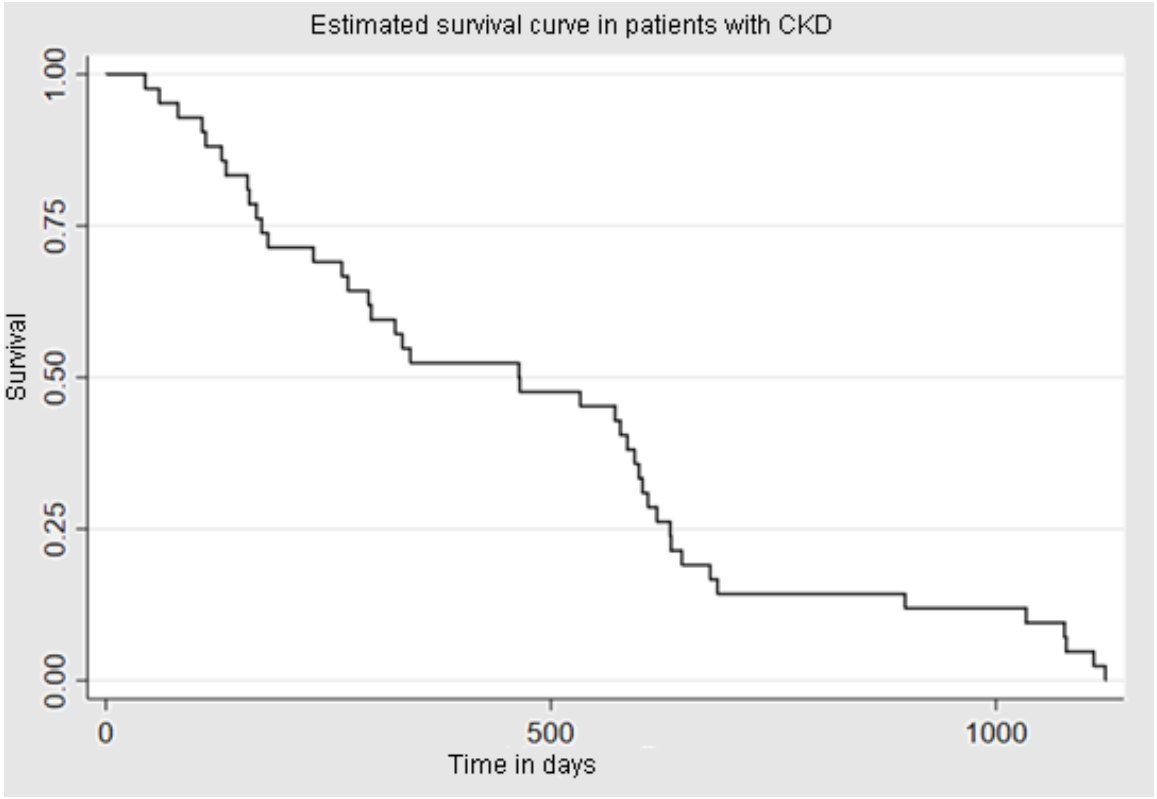

FIGURE 3 - Estimated Kaplan-Meier survival curve over 3 years of the study.

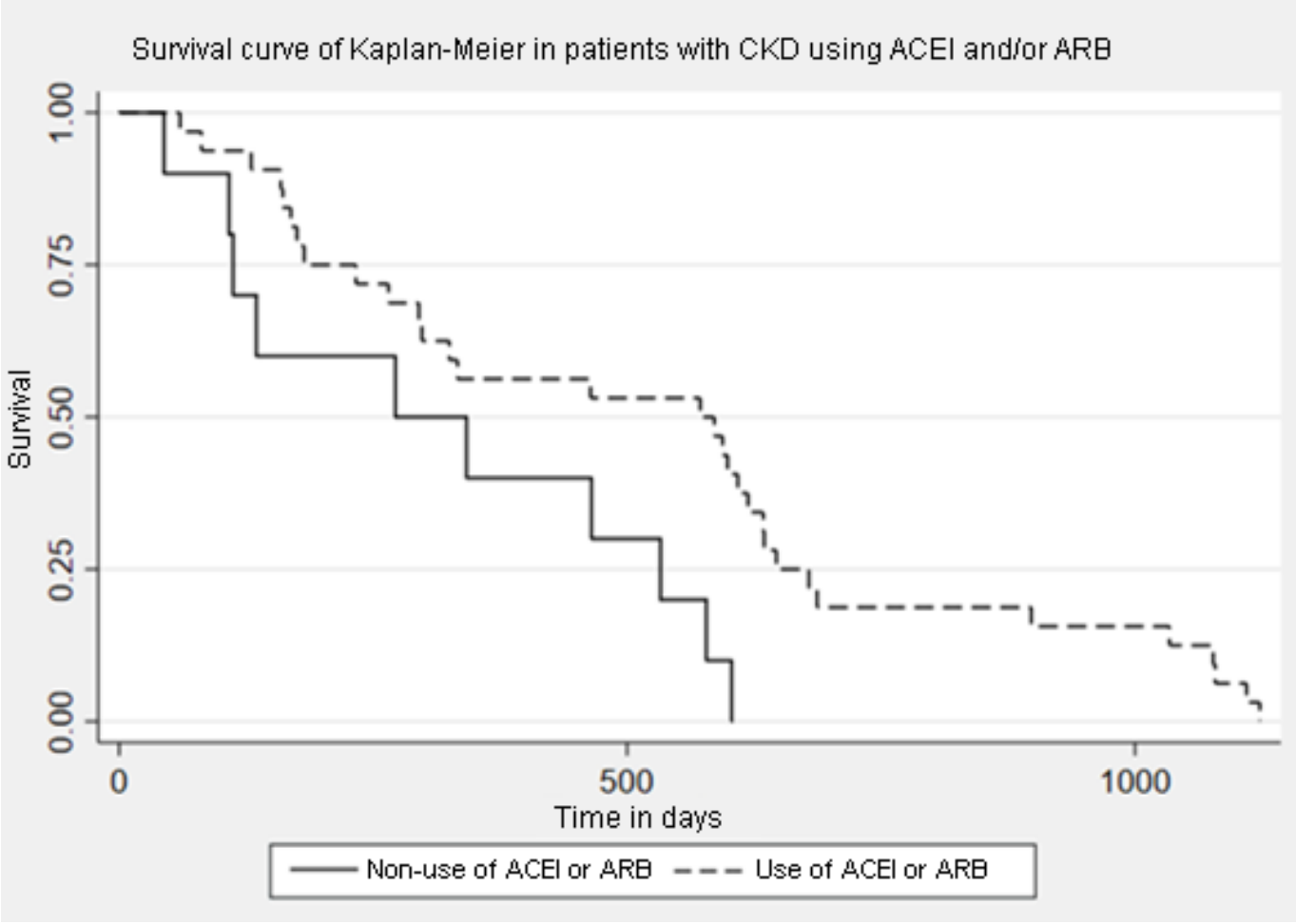

FIGURE 4 - Survival curves estimated by the Kaplan-Meier methods in patients with chronic kidney disease, by exposure or not to the use of ACE inhibitors or ARB.

DISCUSSION

When we compared patients who progressed to the RRT or death outcome with those who did not progress in three years, we observed that those exposed to the nephroprotective drugs (ACE inhibitors or ARB), had a lower risk of progression for the studied outcome and longer survival when compared to those not exposed to these drugs. In contrast, the use of omeprazole or hydrochlorothiazide increased the chances for the outcome of the onset of RRT or death. These help to reinforce the importance of including nephroprotective drugs in the conservative treatment of CKD and the non-use of nephrotoxic drugs. Despite the promising role of diuretics in CKD, their use is associated with adverse renal outcomes and little is discussed about this in clinical practice (Ministério da Saúde, 2014).

Most participants (79.8 %) in the cohort used ACE inhibitors or ARB. When compared with other studies conducted in patients with CKD in Brazil, a similar frequency was found in the study by Pereira and collaborators (2012) (77 %), and higher than the work of Peres and Bettin (2015) (45.6 %). Drugs that block the renin-angiotensin system, such as ACE inhibitors and ARB, are widely prescribed in health services. Losartan, the main representative of ARB, was the drug most used by SUS primary care users in 2015 (Costa *et al.,* 2017). According to systematic reviews published in 2008 and 2011, comparative trials of ACE inhibitors versus ARB did not show significant differences between these agents with regard to cardiovascular and renal protection (Kunz *et al.,* 2008; Maione *et al.,* 2011). ACE inhibitors and ARB have independent

renal and non-fatal cardiovascular benefits, and the choice between one class and another should be based on patient tolerability, pharmacoeconomic, and access issues (Kunz *et al.,* 2008).

In this study, the use of the ACE inhibitors or ARB classes was listed as a protective factor for progression to RRT or death and longer patient survival. This corroborates the findings of other studies in the literature (Jafar *et al.,* 2001; Schaefer, Wühl, 2012). Pereira *et al.* (2012) found that not using ARB increased the chance of death four times in patients with non-dialysis CKD (Relative Risk (RR) 4.18; CI 1.34–12.9). In a meta-analysis carried out from 11 clinical trials, it was demonstrated that the use of ACE inhibitors by patients with CKD was a protective factor for progression to RRT (RR 0.69; CI, 0.51 to 0.94) (Jafar *et al.,* 2001). The advantages of using these drugs go beyond the antihypertensive effect, since they have antiproteinuric properties that prevent the progression of CKD, reduce cardiovascular events, and mortality from all causes, being recommended by the CKD guidelines for nephroprotection (Sarmento *et al.,* 2018; Varallo *et al.,* 2018). Therefore the results of the present study reinforce the need to use nephroprotective drugs in the management of chronic renal patients undergoing conservative treatment.

However, the use of omeprazole, the main representative of the class of proton pump inhibitors (PPIs), had a prevalence of 34.7 % and was associated with a six times higher risk of evolution to RRT or death (HR 6.25; CI: 2.32 - 16.78). The prescription of omeprazole for the prevention and treatment of polypharmacy-related digestive disorders is common, especially in elderly patients. Several studies have associated the use of omeprazole and other PPIs with the development of acute interstitial nephritis, acute kidney injury, and reduced GFR, which could be due to inflammation due to the immune response caused by the accumulation of PPIs (Lazarus *et al.,* 2016; Yang *et al.,* 2017; Hung *et al.,* 2018; Morschel, Mafra, Eduardo, 2018; Varallo *et al.*, 2018; Hart *et al.*, 2019; Yang, Juang, Liao, 2019; Guedes *et al.*, 2020). Considering the findings of the present study and the literature, it is necessary to investigate, through more robust studies, the use of these drugs in patients with CKD, because the use of PPIs, although effective in their effect of controlling gastric disorders, can be a factor for worsening kidney function.

Regarding the use of hydrochlorothiazide, this study demonstrated a 2.8 times greater risk of needing RRT or progression to death when compared to those not exposed (HR 2.80; CI 1.12 - 7.05). In a cohort conducted with 322 patients with non-dialysis CKD, it was demonstrated that the use of diuretics was associated with adverse renal outcomes, such as a decline in GFR and an increased risk of starting RRT (Khan *et al.,* 2017). Other studies have reported that diuretic therapy is detrimental to renal function and causes a significant increase in serum creatinine values (Brown *et al.*, 2000; ALLHAT, 2002). The mechanism by which hydrochlorothiazide causes kidney damage is unclear. It is known that diuretics can cause apoptosis in distal nephron tubular cells. In addition, hypokalemia, which can be induced with the use of these drugs, can lead to renal hypertrophy and tubulointerstitial fibrosis (Choudhury, Ahmed, 2006; Cotter, *et al.,* 2008). In contrast, hydrochlorothiazide is one of the most used drugs in the treatment of SAH, being the treatment of choice in some cases (MS, 2014). Savage *et al.*, (2020) point out that diuretics are often indicated to solve adverse reactions caused by calcium channel blockers, such as edema. Therefore, randomized controlled studies are suggested to investigate the association between the use of hydrochlorothiazide and renal outcomes in patients with non-dialysis CKD.

Most of the individuals in this cohort (83.4 %) were elderly, which is in line with national and international studies that report that the prevalence of CKD is higher in older individuals (Marinho *et al.,* 2017; Lascasas *et al.,* 2019). Among the variables associated with the progression of CKD to RRT or death, only age (HR: 1.06; CI 1.02 - 1.11) is considered an unmodifiable risk factor. Pereira and collaborators (2012) also observed that age (RR 1.09; 95 % CI, 1.04-1.15; $p < 0.001$) is a risk factor for the development of death in patients with non-dialysis CKD. The elderly suffer an average annual decline of 1 to 2 mL/min/1.73 m^2 as part of the renal aging process (Bochud, 2015). According to Denic *et al.* (2017), healthy aging is associated with a 50 % decline in the total number of glomeruli, and therefore, "old kidneys should not be equated with 'sick' kidneys". Therefore,

caution must be taken in the management of care in these patients (Glassock, Denic, Rule, 2017).

The main comorbidities presented by the participants in this cohort were SAH, DM, anemia, and dyslipidemia. SAH and DM were identified as the main primary factors for CKD according to information in the medical records, while anemia was one of the complications of CKD. In the same way, SAH can be secondary to kidney disease, which can explain the large number of patients with hypertension (90.2 %). Furthermore, the prevalence of SAH increases in old age and considering our population of study, this could be another explanation to the data found. Anemia sets in due to impaired production of the hormone erythropoietin, which is produced by the kidneys and is responsible for the synthesis of erythrocytes (Stenvinkel, 2010; Silva *et al.*, 2011). Dyslipidemia was the only comorbidity that showed a significant difference between the groups that progressed or not for the assessed outcome, with the group that did not progress with a higher proportion of this diagnosis. Normally, patients with CKD showed physiological and biochemical changes that alter lipid profiles (Peres, Bettin, 2015). However, as dyslipidemia is a traditional cardiovascular risk factor, it can cause affected individuals to have greater health care (Lascasas *et al.,* 2019). It is possible that patients who progressed were more aggressively treated with statins. However, due to the fact that we collected information in secondary data which had a lack of information regarding all the drugs in use of the patients, we cannot state this. In the treatment of CKD, the management of these comorbidities is essential to prevent disease progression.

The three-year mortality rate found in this study was 20.2 %. Cardiovascular disease (CVD) is the leading cause of early death in patients with CKD (Ripley, 2009). In the United States, between 1995 and 2004, the rate of hospitalization for all causes among patients with CKD remained stable, but the rate of hospitalization for cardiovascular causes increased by 8.0 % (USRDS, 2006). Anemia and dyslipidemia, one of the most prevalent comorbidities in this study, are also factors associated with mortality from CVD and progression of CKD (Lascasas *et al.,* 2019; Thorp *et al.,* 2009).

Among the limitations of the study, it is mentioned that the retrospective cohort design with the use of secondary data, may favor the occurrence of information bias, which was minimized using two sources for checking the data (medical records and the Integrated Health System). In addition, the study was conducted only with patients referred by the nephrologist, generating a selection bias, which selects patients with possibly better care management. Furthermore, it was not possible to separate the patients according to proteinuria due to the lack of classification standard in the city of the study. Regarding the association found with the use of omeprazole, despite being well described in the literature, it is noteworthy that many patients who use PPIs have multiple comorbidities and use polypharmacy, which could influence the result obtained, which was not evaluated because we had only secondary data without access to all the drugs being used by the patients, which could underestimate the data. Another limitation was the impossibility of identifying the patients' cause of death and the presence of CVD because of the lack of information in the secondary data. In several variables of "Use of other drugs", it is possible that statistical significance was not found due to the small sample size. In contrast, among the potentialities of this study, it stands out to be a cohort inserted in the real world of the Brazilian patients with CKD stages 3A to 5-ND all treated in secondary care in the SUS, where we do not have government data of these patients. Thus it was possible to analyze how the disease is being treated in this context and how the drugs are influencing its progression.

CONCLUSION

This study showed that the use of nephroprotective drugs such as ACE inhibitors or ARB, were protective factors for the onset of RRT or the occurrence of death in patients with CKD followed up in a secondary care service. In contrast, age and the use of omeprazole and hydrochlorothiazide were associated with the occurrence of these outcomes. These results reinforce the importance of rational management of pharmacotherapy for patients with CKD. The results regarding the use of omeprazole and hydrochlorothiazide reinforce other studies reported in the literature, however they need to be interpreted with

caution, since clinical trials are necessary to confirm this association.

CONFLICTS OF INTEREST

None

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