Non-linear progression of chronic kidney disease and associated factors in hypertensive patients: a 4-year cohort study

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Abstract

Background

Recent studies suggest that the progression of chronic kidney disease (CKD) is not linear, but we do not have clear evidence on this issue, especially in hypertensive patients. We sought to evaluate the progression of CKD and associated factors over four years in a cohort of hypertensive patients.

Methods

We conducted a prospective cohort study during the years 2012 and 2016, with hypertensive patients diagnosed with CKD (n = 113). The progression of CKD was assessed through the evolution of the glomerular filtration rate (GFR) and the change in the stage of CKD between 2012 and 2016. Sociodemographic, economic, lifestyle, clinical, anthropometric, and biochemical variables were evaluated. The strength of the association between CKD progression and explanatory variables was assessed by odds ratio (OR) and their respective 95% confidence intervals using univariate and multivariate logistic regression.

Results

Regarding progression, 78.1% of the CKD patients did not progress over four years. When assessing the CKD trajectory (2012–2016) through the evolution of GFR, there was a mean reduction of 1.3 mL/min/1.73m² in four years. In the group that progressed, there was a reduction of 13 mL/min/1.73m², while in the group that did not progress, there was an increase of 2 mL/min/1.73m². In the multivariate analyses, age (p = 0.047), diabetes mellitus (DM) (p = 0.042), and urea (p = 0.050) were independently associated with CKD progression.

Conclusions

The findings of the present study showed a non-linear progression of CKD over the four years, contrary to what is traditionally expected. Age, DM and urea were independently associated with CKD progression.

Introduction

Traditionally, chronic kidney disease (CKD) is characterized by a progressive loss of renal function, often manifested by a decline in glomerular filtration rate (GFR), over a long period of time [1]. However, recent studies [2–4] suggest that the progression of CKD is not linear. Many patients suffer from the non-progressive or slowly-progressive form of the disease and will never develop terminal kidney disease. Conversely, some patients evolve rapidly to terminal kidney failure [4].

Complex interactions that involve several clinical, genetic, and environmental factors determine the progression of CKD. The main factors are age, gender, arterial hypertension (AH), diabetes mellitus (DM), proteinuria, anemia, metabolic complications, obesity, smoking, dyslipidemia, and genetic factors [5, 6].

To develop effective strategies to delay or prevent the progression of CKD, it is important to evaluate the changes that occur in the GFR over time, in order to know more about the disease history. Previous studies on the prognosis of CKD have not provided clear evidence on this issue. Epidemiological studies on CKD were not longitudinal [7, 8], and the longitudinal data did not provide estimates of change in GFR [9–13]. In addition, some studies have not verified if the reduced GFR persisted for three months or more, as required by the definition of CKD [8, 10], thus generating bias by the inclusion of patients with reversible acute renal insufficiency. Other studies [3, 4] did not show the evolution of GFR through repeated pre-scheduled measures for the same time interval during the monitoring period, which would be the ideal design according to Eriksen and Ingebretsen [14]. Finally, recent studies have not investigated the factors associated with the progression of CKD [2–4, 15].

Following what was proposed as the ideal design, the objective of this longitudinal observational study was to evaluate the progression of CKD and associated factors over four years in a cohort of hypertensive patients.

Methods

Study design and subjects

We conducted a prospective cohort study during the years 2012 and 2016, with hypertensive patients accompanied by primary health care teams from the municipality of Porto Firme, Minas Gerais, Brazil.

The inclusion criteria in the study were individuals aged 18 years or older with AH and who agreed to participate in the study after due clarification. The exclusion criteria were individuals with severe clinical conditions who needed specialized care, pregnant women, individuals with a history of alcohol and/or drug abuse, and individuals with a diagnosis of established CKD.

At baseline, there were 697 hypertensive patients registered in the primary care information system. The sample was defined considering the reference population with AH in 2012 of the municipality (n=697), a prevalence of 50% of the phenomenon studied, 5% sample margin of error, 10% of refusals and/or losses, 20% to control confounders, and 95% confidence level. The sample calculation resulted in a minimum sample of 248 individuals. The final study sample consisted of 293 individuals. The sample calculation was performed using the Statcalc program of Epi-Info® version 7.2.

A previous study [16] screened 293 individuals for CKD through the GFR estimated by the formula *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) and by analysis of proteinuria and albuminuria in urine of 24 hours. Of these, 113 individuals were diagnosed with CKD. CKD patients were individuals with GFR < 60 mL/min/1.73m², with confirmation three months after the initial diagnosis.

In the present study, patients diagnosed with CKD (n = 113) were followed for four years. At the end of the follow-up, there were 96 patients with CKD, which corresponds to 85% of those initially evaluated. The loss of 17 individuals was due to death (n=14), change of town (n=3), and declined participation (n=4).

During the follow-up, six measurements of GFR and albuminuria were performed. The progression of CKD was assessed through the evolution of the GFR and the change in the stage of CKD between 2012 and 2016.

Data collection

Data collection occurred through individual interviews and anthropometric and biochemical evaluations. As an instrument of data collection, a semi-structured interview guide was used, addressing sociodemographic and economic (gender, age, civil status, education, and family income), lifestyle (tobacco use, alcohol intake, and physical activity), and clinical (DM and time with AH) variables. Physical activity was assessed using the short version of the World Health Organization (WHO) International Physical Activity.

In relation to anthropometric measurements, weight, height, and waist circumference (WC) were assessed. The weight was obtained by means of electronic balance, with a capacity of 150 kg and division of 50 grams; the height was measured using a portable anthropometer, composed by a metallic platform for positioning the individuals and a removable wooden column containing a millimeter tape and cursor for reading, according to the techniques proposed by Jelliffe [17]. The body mass index (BMI) was calculated by the ratio between weight and squared height, and classified according to the criteria of the WHO [18] for adults and Lipschitz [19] for the elderly. The WC measurement was performed using an inextensible tape and measured in centimeters, at the midpoint between the iliac crest and the external face of the last rib. The values were classified in relation to the risk for cardiovascular diseases and metabolic complications according to the cutoff points proposed by the WHO [18].

Regarding the biochemical variables, serum creatinine and albuminuria were evaluated to analyze renal function. Albuminuria was considered abnormal when the value was ≥ 30 mg/24h, as described by Kidney Disease Improving Global Outcomes (KDIGO) [1]. The GFR was estimated from the CKD-EPI formula, currently recommended by the KDIGO [1] and the Brazilian Ministry of Health [20]. CKD stages were classified as follows [1]: (1) GFR 90 mL/min/1.73 m^2; (2) GFR between 60 and 89 mL/min/1.73 m^2; (3A) GFR between 45 and 59 mL/min/1.73 m^2; (3B) GFR between 30 and 44 mL/min/1.73 m^2; (4) GFR between 15 and 29 mL/min/1.73 m^2; (5) GFR < 15 mL/min/1.73 m^2. To determine the progression of CKD, we considered the change in the stages over the four years (2012–2016). Patients were included in the progression group if the CKD stage had progressed. Patients were included in the non-progression group if they maintained the same CKD stage or if their condition had improved to an earlier CKD stage.

On the scheduled day, participants attended the laboratory accredited for the blood and urine collection. The participants were instructed to maintain the usual diet during the day and fast for 12 hours before

collection. The analysis of the biological material was performed in a private laboratory, using commercial kits.

Statistical analysis

The normality of the data was tested using the Kolmogorov–Smirnov test. Continuous variables were described as mean and standard deviation, and categorical variables were expressed as frequencies. Differences in baseline characteristics were tested for statistical significance with a t test for continuous data and chi-square test for categorical variables. The strength of the association between CKD progression and explanatory variables was assessed by odds ratio (OR) and their respective 95% confidence intervals using univariate and multivariate logistic regression. For data analysis, the software SPSS Statistics for Windows (version 20.0) was used, and the statistical significance was set to $p \leq 0.05$.

Results

In relation to the sociodemographic and economic characteristics of the studied population, the majority was female, elderly, living with a partner, and with low education and low income. Regarding lifestyle, 67.7% had never smoked, 94.8% did not use alcohol, and 58.3% were physically active. Most participants did not have DM and discovered AH less than 10 years ago. Regarding nutritional status, 61.5% were overweight and 85.4% had cardiovascular risk. The biochemical parameters are described in Table 1. Regarding progression, 78.1% (n=75) of the CKD patients did not progress over four years. There was a statistically significant difference between the progression and non-progression groups for DM (p=0.042) and urea (p=0.029).

Table 1

In Table 2, when assessing the CKD trajectory (2012–2016) through the evolution of GFR, there was a mean reduction of 1.3 mL/min/1.73m² in four years, which corresponds to 0.32 mL/min/1.73m² per year. In the group that progressed, there was a reduction of 13 mL/min/1.73m² in four years or 3.25 mL/min/1.73m² per year in the GFR, while in the group that did not progress, there was an increase of 2 mL/min/1.73m² in four years or 0.5 mL/min/1.73m² per year, indicating a non-linear trajectory of the GFR over time. It is noteworthy that 12.5% (n=12) of the participants showed rapid progression of CKD over a year (reduction in GFR greater than 3 mL/min/1.73m² per year).

Table 2

Graph 1 illustrates the non-linear trajectory of the GFR during the years 2012 and 2016 in the progression and non-progression groups. In 2016, it is possible to observe an increase in the GFR for the non-progression group.

Graph 1

In the multivariate analyses, presented in Table 3, age ≥ 75 years (p=0.047), DM (p=0.042), and urea (p=0.050) were independently associated with CKD progression.

Table 3

Discussion

The findings of the present study showed a non-linear progression of CKD over the four years. During follow-up, there was a reduction of 1.3 mL/min/1.73m² in GFR. In the progression group, there was an average reduction of 13 mL/min/1.73m², which characterizes rapid progression. On the other hand, in the non-progression group, there was an increase of 2 mL/min/1.73m² in GFR, contrary to what is traditionally expected, which is a GFR reduction (slow or fast) or maintenance.

Xie et al. [15] characterized three different GFR trajectory classes of people entering CKD stage 4 (2008–2013): consistent slow decline with absolute GFR change of − 2.45 mL/min/1.73 m^2 per year; consistent fast decline and GFR change of − 8.60 mL/min/1.73 m^2 per year; and early nondecline and late fast decline with GFR change of − 0.4 mL/min/1.73 m^2 per year in years 1 to 3 and − 7.98 and − 21.36 mL/min/1.73 m^2 per year in years 4 and 5, respectively. The study *Prevention of Renal and Vascular End-Stage Disease*, carried out with 6,894 people during four years, found an estimated GFR loss of 0.2 mL/min/1.73m² in the impaired renal function group [21], similar to the study by Inaguma et al. [22] that showed an annual average decrease of 0.36 mL/min/1.73 m^2 in GFR. Another study with a median follow-up of 31 months (2.5 years) with patients with estimated GFR less than 30 mL/min/1.73m² showed a decline in GFR of 2.65 mL/min/1.73m² per year [23]. Therefore, different situations are observed in relation to GFR over time, and it is not possible to establish a pattern. In the present study, we can establish two situations: a group that progressed rapidly (3.25 mL/min/1.73m² per year) and another group that maintained a similar GFR and/or increased the GFR in relation to the baseline (non-progression).

Thus, an important finding of this study was the non-linear variation in the values of GFR throughout time, with increased or decreased GFR. The traditional paradigm of GFR progression among patients with CKD shows a steady and almost linear decline over time [3, 14]. In contrast to the traditional paradigm, many patients with CKD have a fast and/or slow progression of the disease or an extended period of non-progression. In the *Modification of Diet in Renal Disease* study, approximately 19% of patients with GFR between 25 and 55 mL/min/1.73m² experienced improvement or stabilization of renal function during the study period of two years [24], which corroborates other studies of great relevance [3, 4, 14, 15, 25].

In addition to the individual biological variation, the analytical variation inherent to the estimation of the GFR from serum creatinine measurements should be considered. Some problems related to determining the serum creatinine are inconstant production of serum creatinine, increasing with intake of meat, creatine, or with excessive muscular effort; the Jaffé creatinine analysis method suffers interference, *in vitro*, positively from cephalosporins and ketone bodies and negatively from bilirubin; enzymatic methods

suffer interference, *in vitro*, from n-acetylcysteine and dipyrone; and creatinine values vary with the presence of simple infections, dehydration, and use of nephrotoxic drugs [26]. Thus, one of the challenges in the use of routine analyses of creatinine to estimate changes in GFR over a long period is to ensure the stability of the test. Although the strict quality control routines protect against major fluctuations, variation in the long term cannot be completely excluded [14].

This study also associated the progression of CKD with sociodemographic, economic, lifestyle, clinical, anthropometric, and biochemical variables. Knowing the associated factors may contribute to the correct identification of CKD and implementation of actions to slow its progression [27]. In the multivariate analyses, age ≥ 75 years, DM, and urea were independently associated with CKD progression.

In the present study, individuals aged ≥ 75 years were eight times more likely to have CKD progression than individuals aged ≤ 68 years. Age is recognized as an independent risk factor for CKD, and the findings of association of this disease with aging are consistent with previous studies [28, 29]. However, in an analysis of a large cohort, older age was associated with slower loss of GFR, although this seemed to be true only at GFR levels < 45 ml/min per 1.73 m² [30]. Conway et al. [31] described similar results in an elderly population with stage 4 CKD. Thus, it appears that there is some other pathological process, likely vascular in etiology, that plays a role in pathogenesis of GFR decline in the elderly [32]. Considering that all individuals in this study have AH, this factor may also be contributing to the progression of CKD. Data from the Boston Longitudinal Study of Ageing suggest that the decline in GFR with increasing age is largely attributable to AH or the presence of comorbidities, such as heart failure and other cardiovascular diseases [33].

Another important factor is DM, which is the leading cause of CKD in the developed world, and people with diabetes and CKD have a greatly increased risk of all-cause mortality, cardiovascular mortality, and kidney failure [34]. In individuals with diabetes, both GFR and albuminuria are important predictors of kidney outcomes. In a recent meta-analysis, compared to the nondiabetic participants, those with diabetes showed a borderline increased hazard for the progression from late-stage CKD to end-stage renal disease (HR 1.16, 95% CI 0.98–1.38) [35]. On the other hand, the study by Levin et al. [23] had the largest study population and enrolled stage 4 to 5 CKD patients, for whom diabetes was reported as a nonsignificant factor (HR 0.82, 95% CI 0.56–1.20; P = 0.30). Previous studies have demonstrated large variation in GFR progression in persons with diabetes [36]. In the present study, individuals with diabetes were 8.74 times more likely to have CKD progression than individuals without diabetes.

In relation to urea, individuals with higher urea levels were 8% more likely to have CKD progression. Its elevation indicates inability of the renal system to purify the blood of nitrogenous products. Fehrman-Ekholm and Skeppholm [37] found a significantly positive correlation between age and urea (p = 0.0019); that is, urea increased with age, which probably reflects the decrease in GFR, which corroborates the data from the present study. Levey [38] highlights that urea is the first used endogenous marker, but it is not completely reliable, as its levels are more vulnerable to changes for reasons unrelated to GFR.

Finally, in individuals who are progressing, the subsequent risk of morbidity and mortality increases exponentially, as well as the costs associated to health. A reduced GFR also associates with a wide range of complications and reduced quality of life. Therefore, it is important to clarify which factors are associated with the CKD progression and are potentially modifiable, in order to intervene early and improve the associated adverse results [25].

There are limitations to this study. There are medications that may be more commonly taken by hypertensive patients that may have an effect on renal function. We were unable to include these in our analysis. Another limitation of the study was the difficulty maintaining consistent calibration of the serum creatinine test over time, and the results are highly sensitive to progression adrift in the assay of creatinine. Despite this, the findings of this study have implications for future researches on CKD. Identifying non-linearity in the progression of the disease suggests a new approach to other studies that investigate the association of risk factors that vary in time with changes in renal function. Thus, a more accurate understanding of the CKD trajectory can help to guide clinical decision making, develop actions of prevention of disease progression, and seek to improve patients' quality of life.

Conclusion

In conclusion, the findings of the present study showed a non-linear progression of CKD over the four years, contrary to what is traditionally expected. We can establish two situations: a group that progressed rapidly and another group that maintained a similar GFR and/or increased the GFR in relation to the baseline (non-progression). Age, DM and urea were independently associated with CKD progression.

Abbreviations

CKD
chronic kidney disease
GFR
glomerular filtration rate
AH
arterial hypertension
DM
diabetes mellitus
WHO
World Health Organization
WC
waist circumference
BMI
body mass index
KDIGO
Kidney Disease Improving Global Outcomes

OR
odds ratio
CKD-EPI
Chronic Kidney Disease Epidemiology Collaboration

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present study was approved by the Human Research Ethics Committee of the Universidade Federal de Viçosa (UFV) under protocol no. 044/2012 and process 1.139.717/2015.

Informed consent was obtained from all individual participants included in the study. As per Resolution 466/2012 of the National Health Council, which regulates research involving human subjects, the participants signed a free and informed statement of consent, which ensured the confidentiality of the data and the anonymity of the participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LSS participated in the design of the study, the collection of the data, the statistical analysis and interpretation of data, the redaction of the article. TRM participated in the design of the study, the statistical analysis and interpretation of data, the redaction of the article. RGS and RMMC participated in the design of the study, the redaction of the article. All authors read and approved the final manuscript.

References

1. Kidney Disease. Improving Global Outcomes (KDIGO) CKD Work. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1–150. http://www.kidney-international.org.
2. Weldegiorgis M, de Zeeuw D, Li L, Parving HH, Hou FF, Remuzzi G, et al. Longitudinal Estimated GFR Trajectories in Patients With and Without Type 2 Diabetes and Nephropathy. Am J Kidney Dis. 2018;71:91–101.
3. Li L, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, et al. Longitudinal Progression Trajectory of GFR Among Patients With CKD. Am J Kidney Dis. 2012;59:504–12. doi:10.1053/j.ajkd.2011.12.009.
4. O'Hare AM, Batten A, Burrows NR, Pavkov ME, Taylor L, Gupta I, et al. Trajectories of Kidney Function Decline in the 2 Years Before Initiation of Long-term Dialysis. Am J Kidney Dis. 2012;59:513–22. doi:10.1053/J.AJKD.2011.11.044.
5. Bastos MG, Kirsztajn GM. Doença renal crônica: importância do diagnóstico precoce, encaminhamento imediato e abordagem interdisciplinar estruturada para melhora do desfecho em pacientes ainda não submetidos à diálise. J Bras Nefrol. 2011;33:93–108. doi:10.1590/S0101-28002011000100013.
6. USRDS. United States Renal Data System (USRD). (2016) Annual Data Report: Epidemiology of Kidney Disease in the United States, National Institutes of Health. 2016.
7. Culleton BF, Larson MG, Evans JC, Wilson PWF, Barrett BJ, Parfrey PS, et al. Prevalence and Correlates of Elevated Serum Creatinine Levels. Arch Intern Med. 1999;159:1785. doi:10.1001/archinte.159.15.1785.
8. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third national health and nutrition examination survey. Am J Kidney Dis. 2003;41:1–12. doi:10.1053/ajkd.2003.50007.
9. Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. Am J Kidney Dis. 2003;42:677–84. doi:10.1016/S0272-6386(03)00916-8.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. N Engl J Med. 2004;351:1296–305. doi:10.1056/NEJMoa041031.
11. Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. J Am Soc Nephrol. 2003;14:2934–41. http://www.ncbi.nlm.nih.gov/pubmed/14569104. Accessed 19 Apr 2018.
12. Iseki K, Ikemiya Y, Fukiyama K. Risk factors of end-stage renal disease and serum creatinine in a community-based mass screening. Kidney Int. 1997;51:850–4. doi:10.1038/ki.1997.119.
13. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal Follow-up and Outcomes among a Population with Chronic Kidney Disease in a Large Managed Care Organization. Arch Intern

Med. 2004;164:659–63.

14. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age. Kidney Int. 2006;69:375–82. doi:10.1038/sj.ki.5000058.
15. Xie Y, Bowe B, Xian H, Balasubramanian S, Al-Aly Z. Estimated GFR Trajectories of People Entering CKD Stage 4 and Subsequent Kidney Disease Outcomes and Mortality. Am J Kidney Dis. 2016;68:219–28.
16. da Silva LS, Cotta RMM, Moreira TR, da Silva RG, Rosa C, de OB, Machado. JC, et al. Hidden prevalence of chronic kidney disease in hypertensive patients: the strategic role of primary health care. Public Health. 2016;140:250–7. doi:10.1016/j.puhe.2016.02.029.
17. Jelliffe DB. Evaluación del estado de nutrición de la comunidad. Ginebra: Organizacion Mundial de la Salud; 1968.
18. World Health Organization. Obesity: preventing and managing the global epidemic : report of a WHO consultation. World Health Organization; 2000.
19. Lipschitz DA. Screening for nutritional status in the elderly. Prim Care. 1994;21:55–67. http://www.ncbi.nlm.nih.gov/pubmed/8197257. Accessed 19 Apr 2018.
20. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Especializada e Temática. Diretrizes Clínicas para o Cuidado ao paciente com Doença Renal Crônica – DRC no Sistema Único de Saúde. Brasília; 2014. https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_clinicas_cuidado_paciente_renal.pdf.
21. Halbesma N, Kuiken D-S, Brantsma AH, Bakker SJL, Wetzels JFM, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–90. doi:10.1681/ASN.2005121352.
22. Inaguma D, Imai E, Takeuchi A, Ohashi Y, Watanabe T, Nitta K, et al. Risk factors for CKD progression in Japanese patients: findings from the Chronic Kidney Disease Japan Cohort (CKD-JAC) study. Clin Exp Nephrol. 2017;21:446–56.
23. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and Risk Factors for Kidney Disease Progression and Death Following Attainment of Stage 4 CKD in a Referred Cohort. Am J Kidney Dis. 2008;52:661–71. doi:10.1053/j.ajkd.2008.06.023.
24. Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. Kidney Int. 1997;51:1908–19. http://www.ncbi.nlm.nih.gov/pubmed/9186882. Accessed 19 Apr 2018.
25. NICE. National Clinical Guideline Centre Chronic kidney. disease (partial update) Early identification and management of chronic kidney disease in adults in primary and secondary care. In: Chronic Kidney Disease. London: National Institute for Health and Care Excellence (UK); 2014.
26. Anderson S, Halter JB, Hazzard WR, Himmelfarb J, Horne FM, Kaysen GA, et al. Prediction, Progression, and Outcomes of Chronic Kidney Disease in Older Adults. J Am Soc Nephrol. 2009;20:1199–209. doi:10.1681/ASN.2008080860.

27. Vejakama P, Ingsathit A, McEvoy M, Attia J, Thakkinstian A. Progression of chronic kidney disease: an illness-death model approach. BMC Nephrol. 2017;18:205. doi:10.1186/s12882-017-0604-8.
28. Ramirez SPB, McClellan W, Port FK, Hsu SIH. Risk factors for proteinuria in a large, multiracial, Southeast Asian population. J Am Soc Nephrol. 2002;13:1907–17.
29. De Jong PE, Brenner BM. From secondary to primary prevention of progressive renal disease: The case for screening for albuminuria. Kidney Int. 2004;66:2109–18.
30. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. Age affects outcomes in chronic kidney disease. J Am Soc Nephrol. 2007;18:2758–65.
31. Conway B, Webster A, Ramsay G, Morgan N, Neary J, Whitworth C, et al. Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease. Nephrol Dial Transplant. 2009;24:1930–7.
32. Arora P, Jalal K, Gupta A, Carter RL, Lohr JW. Progression of kidney disease in elderly stage 3 and 4 chronic kidney disease patients. Int Urol Nephrol. 2017;49:1033–40.
33. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E. Renal function in the elderly: Impact of hypertension and cardiac function. Kidney Int. 1997;51:1196–204.
34. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PWF, Levy D. Predictors of New-Onset Kidney Disease in a Community-Based Population. J Am Med Assoc. 2004;291:844–50.
35. Tsai W-C, Wu H-Y, Peng Y-S, Ko M-J, Wu M-S, Hung K-Y, et al. Risk Factors for Development and Progression of Chronic Kidney Disease. Med (Baltim). 2016;95:e3013.
36. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive decline in estimated glomerular filtration rate in patients with diabetes after moderate loss in kidney functiond even without albuminuria. Diabetes Care. 2019;42:1886–94.
37. Fehrman-Ekholm I, Skeppholm L. Renal Function in the Elderly (> 70 Years Old) Measured by Means of Iohexol Clearance, Serum Creatinine, Serum Urea and Estimated Clearance. Scand J Urol Nephrol. 2004;38:73–7. doi:10.1080/00365590310015750.
38. Levey AS. Measurement of renal function in chronic renal disease. Kidney Int. 1990;38:167–84.

Tables

Table 1. Sociodemographic, economic, lifestyle, clinical, anthropometric, and biochemical characteristics of the patients, according to progression of CKD, 2012–2016.

Variables		Total	Progression		p
			Yes (n=21)	No (n=75)	
Gender	Female	71 (74,0)	14 (66.7)	57 (76.0)	0.389
	Male	25 (26,0)	7 (33.3)	18 (24.0)	
Age (years)	≤ 68	32 (33.3)	4 (19.0)	28 (37.3)	0.286
	69 - 75	35 (36.5)	9 (42.9)	26 (34.7)	
	≥ 75	29 (30.2)	8 (38.1)	21 (28.0)	
Civil status	With a partner	56 (58.3)	11 (52.4)	45 (60.0)	0.531
	No partner	40 (41.7)	10 (47.6)	30 (40.0)	
Education	Elementary School	52 (54.2)	10 (47.6)	42 (56.0)	0.496
	Illiterate	44 (45.8)	11 (52.4)	33 (44.0)	
Family income (minimum wage)	> 3	8 (8.3)	3 (14.3)	5 (6.7)	0.264
	< 3	88 (91.7)	18 (85.7)	70 (93.3)	
Tobacco	Never smoked	65 (67.7)	13 (61.9)	52 (69.3)	0.520
	Smoker or ex-smoker	31 (32.3)	8 (38.1)	23 (30.7)	
Alcohol intake	No	91 (94.8)	19 (90.5)	72 (96.0)	0.314
	Yes	5 (5.2)	2 (9.5)	3 (4.0)	
Physical Activity	Active	56 (58.3)	16 (76.2)	40 (53.3)	0.060
	Not active	40 (41.7)	5 (23.8)	35 (46.7)	
Diabetes Mellitus	No	75 (78.1)	13 (61.9)	62 (82.7)	0.042*
	Yes	21 (21.9)	8 (38.1)	13 (17.3)	
Time with AH	< 10 years	50 (52.1)	9 (42.9)	41 (54.7)	0.338
	> 10 years	46 (47.9)	12 (57.1)	34 (45.3)	
Overweight	No	37 (38.5)	6 (28.6)	31 (41.3)	0.288
	Yes	59 (61.5)	15 (71.4)	44 (58.7)	
Cardiovascular Risk	No	14 (14.6)	2 (9.5)	12 (16.0)	0.457
	Yes	82 (85.4)	19 (90.5)	63 (84.0)	
Albuminuria	< 30 mg/24h	66 (68.8)	11 (52.4)	55 (73.3)	0.067
	≥ 30mg/24h	30 (31.2)	10 (47.6)	20 (26.7)	

CKD stage	3a	85 (88.5)	18 (85.7)	67 (89.3)	0.622
	3b	9 (9.4)	2 (9.5)	7 (9.3)	
	4	2 (2.1)	1 (4.8)	1 (1.3)	
Glucose	Mean (sd)	109.6 (34.3)	116.9 (46.8)	107.5 (30.0)	0.393
Total cholesterol	Mean (sd)	200.7 (38.1)	199.6 (36.1)	201.0 (38.9)	0.881
HDL cholesterol	Mean (sd)	48.6 (9.3)	50.8 (7.2)	48.0 (9.7)	0.155
LDL cholesterol	Mean (sd)	122.6 (31.4)	119.0 (29.9)	123.6 (32.0)	0.545
Tryglicerides	Mean (sd)	149.4 (78.0)	149.0 (60.8)	149.6 (82.6)	0.971
Uric acid	Mean (sd)	6.22 (5.0)	5.7 (1.2)	6.4 (5.6)	0.363
Urea	Mean (sd)	43.2 (9.4)	47.5 (9.9)	42.0 (9.0)	0.029*

*p≤0.05

Table 2. GFR evolution over four years in a cohort of CKD patients, 2012–2016.

GFR (mL/min/1.73m²)	Total	Progression – media (dp)		p
		Yes	No	
2012	51.1 (7.4)	49.2 (10.1)	51.6 (6.5)	0.193
2016	49.8 (11.3)	36.2 (9.0)	53.6 (8.6)	<0.001
Difference (2012-2016)	1.3 (9.8)	13.0 (7.7)	- 2.0 (7.7)	<0.001

Table 3. Association of sociodemographic, economic, lifestyle, clinical, anthropometric, and biochemical variables with CKD progression, 2012–2016.

Variables		Univariate analysis		Multivariate analysis	
Gender	Female	1 (ref.)	0.391	1 (ref.)	0.578
	Male	1.58 (0.55-4.52)		0.52 (0.05-5.20)	
Age (years)	≤ 68	1 (ref.)	0.303	1 (ref.)	0.134
	69 - 75	2.42 (0.66-8.83)		2.79 (0.42-18.49)	0.286
	≥ 75	2.66 (0.70-10.05)		8.77 (1.02-75.03)	0.047*
Civil status	With a partner	1 (ref.)	0.532	1 (ref.)	0.145
	No partner	1.36 (0.51-3.60)		3.69 (0.63-21.39)	
Education	Elementary school or more	1 (ref.)	0.497	1 (ref.)	0.986
	Illiterate	1.40 (0.51-3.69)		0.98 (0.23-4.10)	
Tobacco	Never smoked	1 (ref.)	0.521	1 (ref.)	0.250
	Smoker or ex-smoker	1.39 (0.50-3.81)		2.49 (0.52-11.18)	
Alcohol intake	No	1 (ref.)	0.329	1 (ref.)	0.669
	Yes	2.52 (0.39-16.21)		0.41 (0.00-22.77)	
Diabetes Mellitus	No	1 (ref.)	0.047*	1 (ref.)	0.042*
	Yes	2.93 (1.01-8.50)		8.74 (1.08-70.59)	
Time with AH	< 10 years	1 (ref.)	0.341	1 (ref.)	0.805
	> 10 years	1.60 (0.60-4.26)		1.20 (0.26-5.46)	
Overweight	No	1 (ref.)	0.292	1 (ref.)	0.407
	Yes	1.76 (0.61-5.04)		1.90 (0.41-8.66)	
Cardiovascular Risk	No	1 (ref.)	0.463	1 (ref.)	0.490
	Yes	1.81 (0.37-8.80)		0.39 (0.02-5.50)	
Glucose		1.00 (0.99-1.02)	0.280	0.99 (0.97-1.01)	0.354
Total cholesterol		0.99 (0.98-1.01)	0.884	1.01 (0.95-1.07)	0.641
HDL cholesterol		1.03 (0.98-1.08)	0.229	1.06 (0.97-1.15)	0.154

LDL cholesterol	0.99 (0.97-1.01)	0.554	0.98 (0.92-1.05)	0.744
Triglycerides[a]	1.00 (0.99-1.00)	0.975	-	-
Uric acid	0.95 (0.76-1.18)	0.649	0.94 (0.73-1.20)	0.641
Urea	1.06 (1.00-1.12)	0.023*	1.08 (1.00-1.18)	0.050*
Albuminúria	1.00 (0.99-1.01)	0.096	1.00 (0.99-1.01)	0.229

[a]Triglycerides did not enter the multivariate model. *p≤0.05

Figures

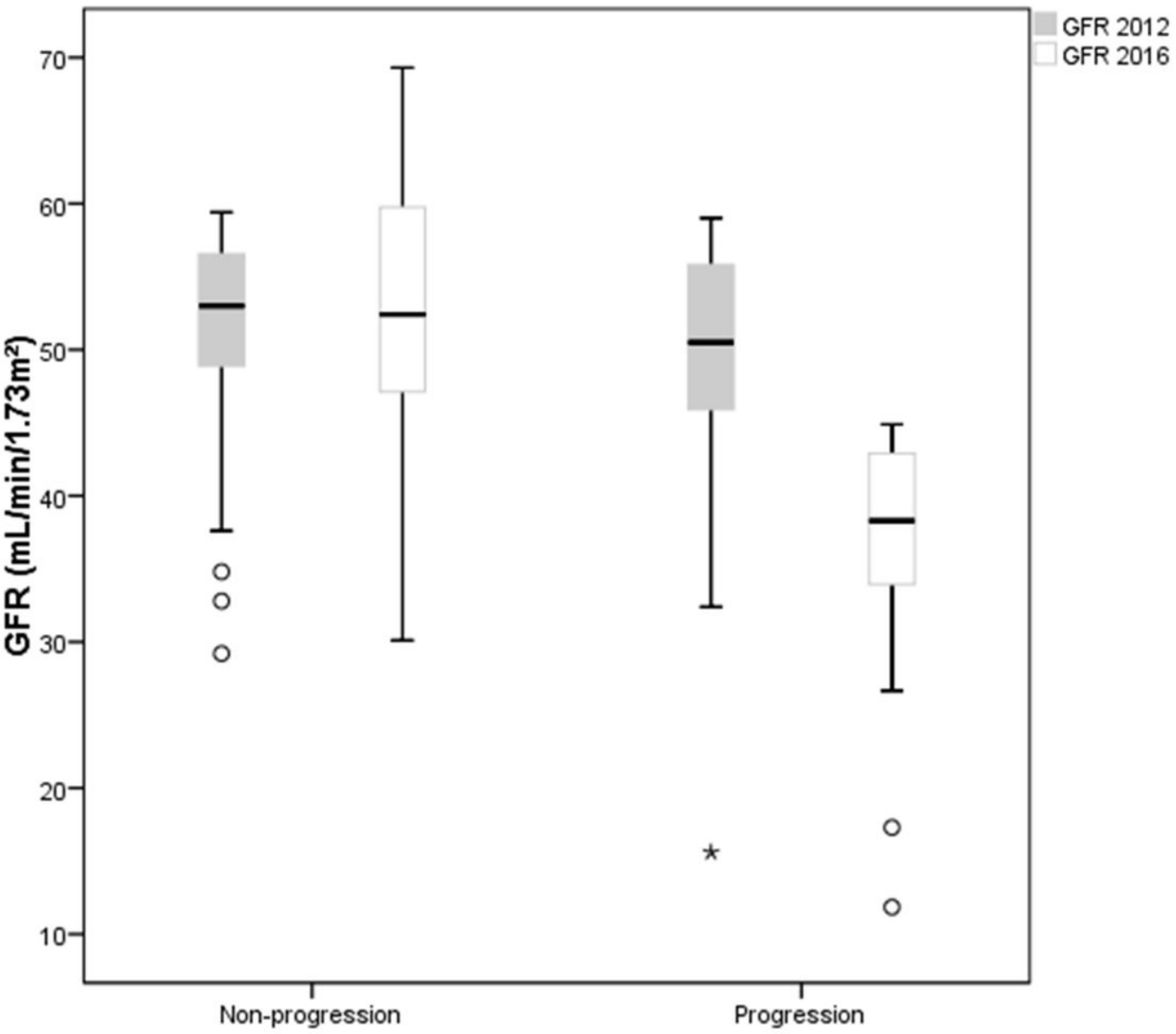

Figure 1

Boxplot of GFR according to progression of CKD, 2012–2016.