PLOS ONE

RESEARCH ARTICLE

Progression of chronic kidney disease among black patients attending a tertiary hospital in Johannesburg, South Africa

Alfred Meremo[1,2]*, **Graham Paget**[1], **Raquel Duarte**[1], **Deogratius Bintabara**[3], **Saraladevi Naicker**[1]

1 Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Science, University of the Witwatersrand, Johannesburg, South Africa, **2** Department of Internal Medicine, School of Medicine & Dentistry, The University Dodoma, Dodoma, Tanzania, **3** Department of Community Medicine, School of Medicine & Dentistry, The University Dodoma, Dodoma, Tanzania

* Alfred.Meremo@wits.ac.za, alfred.meremo@udom.ac.tz

Citation: Meremo A, Paget G, Duarte R, Bintabara D, Naicker S (2023) Progression of chronic kidney disease among black patients attending a tertiary hospital in Johannesburg, South Africa. PLoS ONE 18(2): e0276356. https://doi.org/10.1371/journal.pone.0276356

Editor: Marcelo Arruda Nakazone, Faculdade de Medicina de São José do Rio Preto, BRAZIL

Received: October 4, 2022

Accepted: January 30, 2023

Published: February 13, 2023

Data Availability Statement: Data cannot be shared publicly because of ethics policy at University of Witwatersrand, the participants signed a consent form, which states that data are exclusively available for professional research staff. Data are available to qualifying organizations and/or individuals from the chairperson of the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (Committee) who is Dr. Clement Penny, who may be contacted by e-mail (Clement.Penny@wits.ac.

Abstract

Background

Chronic kidney disease (CKD) is a major public health issue worldwide and is an important contributor to the overall non-communicable disease burden. Chronic kidney disease is usually asymptomatic, and insidiously and silently progresses to advanced stages in resource limited settings.

Methodology

A prospective longitudinal study was carried out on black patients with CKD attending the kidney outpatient clinic at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in South Africa, between September 2019 to March 2022. Demographic and clinical data were extracted from the ongoing continuous clinic records, as well as measurements of vital signs and interviews at baseline and at follow up. Patients provided urine and blood samples for laboratory investigations as standard of care at study entry (0) and at 24 months, and were followed up prospectively for two (2) years. Data were descriptively and inferentially entered into REDcap and analysed using STATA version 17, and multivariable logistic regression analysis was used to identify predictors of CKD progression.

Results

A total of 312 patients were enrolled into the study, 297 (95.2%) patients completed the study, 10 (3.2%) patients were lost to follow and 5 (1.6%) patients died during the study period. The prevalence of CKD progression was 49.5%, while that of CKD remission was 33% and CKD regression was 17.5%. For patients with CKD progression the median age at baseline was 58 (46–67) years, the median eGFR was 37 (32–51) mL/min/1.73 m^2, median urine protein creatinine ratio (uPCR) was 0.038 (0.016–0.82) g/mmol and the median haemoglobin (Hb) was 13.1 (11.7–14.4) g/dl; 95.2% had hypertension, 40.1% patients had diabetes mellitus and 39.5% had both hypertension and diabetes mellitus. Almost half (48.3%) of patients with CKD progression had severely increased proteinuria and 45.6% had

za) for researchers who meet the relevant ethics criteria for access to these data.

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: CKD, chronic kidney diseases; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; CKD-EPI, chronic kidney disease epidemiology collaboration; ESKD, end stage kidney disease; T2DM, Type 2 Diabetes Mellitus; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectroscopy; uPCR, urine protein creatinine ratio; CCBs, calcium channel blockers; ACEIs, angiotensin converting enzyme inhibitors; ARBs, Aldosterone receptors blockers; KDIGO, kidney disease improving global outcomes; NCDs, non-communicable diseases; SSA, sub Saharan Africa; UK, United Kingdom; USA, United States of America.

anaemia. Variables associated with higher odds for CKD progression after multivariable logistic regression analysis were severely increased proteinuria (OR 32.3, 95% CI 2.8–368.6, P = 0.005), moderately increased proteinuria (OR 23.3, 95% CI 2.6–230.1, P = 0.007), hypocalcaemia (OR 3.8, 95% CI 1.0–14.8, P = 0.047), hyponatraemia (OR 4.5, 95% CI 0.8–23.6, P = 0.042), anaemia (OR 2.1, 95% CI 1.0–4.3, P = 0.048), diabetes mellitus (OR 1.8, 95% CI 0.9–3.6, P = 0.047), elevated HbA1c (OR 1.8, 95% CI 1.2–2.8, P = 0.007) and current smoking (OR 2.8, 95% CI 0.9–8.6, P = 0.049).

Conclusion

Our study identified a higher prevalence of CKD progression in a prospective longitudinal study of black patients with CKD compared with literature reports. CKD Progression was associated with proteinuria, diabetes mellitus, elevated HbA1c, anaemia, hypocalcaemia, hyponatraemia and current smoking in a cohort of black patients with CKD who had controlled hypertension and diabetes mellitus at baseline.

Introduction

The global prevalence of chronic kidney disease (CKD) has been progressively increasing and is a significant risk factor for cardiovascular disease morbidity and mortality [1, 2]. The burden of CKD is more prominent in low- and lower-middle-income countries (LLMICs) than in high-income countries (HICs) with a higher prevalence among those disadvantaged and indigenous communities who have less/ limited access to health care [1, 3]. The global increase in CKD is driven by the increasing prevalence of diabetes mellitus, hypertension and obesity [4, 5]. Studies have shown that African-Americans have a 2- to 4-fold higher risk for end-stage kidney disease (ESKD) than their white counterparts requiring renal replacement therapy [6, 7]. Individuals of black ethnicity due to their genes, including the presence of *APOL*1 high-risk genotypes, are at higher risk of increased serum creatinine levels, lower eGFR, more rapid CKD progression and death due to social, economic and medical inequities [8, 9]. Studies have reported the prevalence of CKD to be 15.8% in Africa, with major cost implications to overburdened healthcare systems [10, 11]. In developing countries, patients with ESKD are increasing in numbers and most die due to poor access to kidney replacement therapies, calling for cost effective preventive strategies to reduce CKD progression [4, 12]. Chronic kidney disease in developing countries also tends to be present in younger people who are unaware of their underlying kidney disease, and very few receive optimal care because of resource constraints [13, 14]. Regardless of the underlying cause of CKD, chronic kidney diseases progress slowly to ESKD due to irreversible nephron loss leading to premature death [15, 16]. Slowing CKD progression, promoting remission, or even regression of CKD, have been based on the control of blood pressure, control of blood sugar, reduction of proteinuria and management of other known risk factors for CKD progression [17, 18]. When CKD progressors are identified reliably and earlier in stages 1 to 3, disease progression can be altered with reduced complications [19, 20]. There is a need to identify those patients with CKD and those who are likely to progress more rapidly, to reduce the number of patients progressing to end-stage kidney disease (ESKD). The aim of this study was to study the prevalence and predictors of CKD progression in a cohort of black patients with satisfactory blood pressure and glycaemic control at baseline attending a tertiary hospital in Johannesburg, South Africa.

Methods

Study design, population and settings

This was a prospective longitudinal study to evaluate the prevalence and predictors of CKD progression among black patients attending the kidney outpatient clinic at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) between September 2019 to March 2022. The CMJAH is a public accredited central hospital with 1088 beds serving patients from across the Gauteng province and nearby provinces in South Africa. CMJAH is also one of the main teaching hospitals for the Faculty of Health Sciences of the University of the Witwatersrand. Johannesburg is the largest city in South Africa and among the largest 50 urban agglomerations in the world. Johannesburg had an estimated population of around 5.9 million in 2021, the most common racial groups include black African (76.4%), White (12.3%), mixed ethnicity (5.6%) and Indian/Asian (4.9%). Inclusion criteria for the study were patients who were >18 years of age, with CKD stages 1–4, who had controlled hypertension (blood pressure < 140/90 mm Hg) and diabetes mellitus (HbA1C < 7%) [21, 22], attending the kidney outpatient clinic for at least 6 months and were able to provide informed consent. Patients who had active infections, active malignancies, autoimmune diseases and who were not black were excluded. Black patients have significantly higher rates of more rapid CKD progression and ESKD than other races [23, 24], hence they were the focus of this study.

Data collection and laboratory procedures

Enrollment occurred between September 2019 to March 2020; consecutive sampling was used to meet the required number of study patients and follow up was conducted between September 2021 to March 2022. Demographic and clinical data including age, gender, weight, height, glycaemic status, history of smoking, aetiology of CKD and medications were extracted from the ongoing continuous clinic records. Face to face interviews at the time of enrolment were recorded in a questionnaire and vital signs measurements were conducted at first enrolment and at follow up. Patients provided blood and urine samples at study entry (0) and at 24 months; patients agreed to have their routine medical records accessed prospectively for two (2) years. Systolic and diastolic blood pressure was measured 3 times, and the average of the second and third measurements was used [25]. Body mass index (BMI) was calculated using the National Health Services (NHS-UK) BMI calculator [26]. Measurements of urinary protein creatinine ratio (uPCR), serum creatinine, electrolytes, HbA1C, white cell count, haemoglobin level, platelets, calcium, phosphate, transferrin and HDL cholesterol were done as standard of care at the time of recruitment and at follow up during a clinic visit. Anaemia was defined as a Hb concentration of < 13.0g/dl in males and < 12.0g/dl in females [27]. Serum creatinine was measured using the isotope dilution mass spectrometry (IDMS) traceable enzymatic assay and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without using the African American correction factor, race adjustment of eGFR in black patients may affect their clinical care contributing to differences in the management of their kidney disease [28, 29]. CKD progression was assessed by a (i) change to a more advanced stage of CKD (ii) greater than 30% reduction of eGFR in two years, whereby percent change in eGFR was calculated as last eGFR–first eGFR/first eGFR x 100 [30] (iii) sustained decline in eGFR of > 4 ml/min/1.73 m^2/year or more [31, 32]. CKD regression was defined by a sustained increase in eGFR of > 4 ml/min/1.73 m^2/year or an improvement in CKD stage at 24 months from baseline [18, 31]. CKD remission was defined by a stable or change in eGFR of < 4 ml/min/1.73 m^2/year from baseline and at 24 months of follow up [18, 32].

Data management and analysis

Study data were collected and entered into *REDCap* (Research Electronic Data Capture) tools [33, 34] hosted at the University of the Witwatersrand and analyzed using STATA version 17 (College Station, Texas, USA). Descriptive statistics were used to summarize demographic and clinical data; continuous variables have been reported as medians with interquartile ranges and Wilcoxon rank-sum test was used for the non-normally distributed variables. Discrete variables have been reported as frequencies and proportions, Pearson's chi-square test was used to test for association between variables and CKD progression. Odd ratios were used to estimate the strengths of association between variables and CKD progression; univariate and multivariate logistic regression models were used to estimate the association of variables and CKD progression. Variables with p-value less than 0.2 on univariate logistic regression models were then fitted into the multivariate logistic regression models with the addition of age and sex as adjusting variables; variables with a p-value of less than 0.05 were considered to have significant strength of association.

Ethical issues

Ethical approval was obtained from the Human Research Ethics Committee of the University of Witwatersrand, Johannesburg (ethics clearance certificate No. M190553). Written informed consent was obtained from each of the participants before enrolment and embarking on data collection.

Results

Demographic and clinical characteristics of the study population

A total of 476 black patients with CKD stages 1–4 attended the CMJAH kidney outpatient clinic during the enrolment period, 164 patients were excluded from the study including 110 patients who had uncontrolled hypertension, 35 patients who had uncontrolled diabetes mellitus, 11 patients who had autoimmune diseases, 6 patients had active infections and 2 patients had active malignancies. Of the 312 patients who were enrolled into the study, 10 (3.2%) patients were lost to follow and 5 (1.6%) patients died, 297 (95.2%) patients completed the study of whom 156 (52.5%) were male and 154 (51.8%) were married. Progression of CKD occurred in 147 (49.5%) patients over 2 years of follow up. The median age was 58 (46–67) years for CKD progressors and 57 (45–66) years for those without CKD progression. Significant variables were the median eGFR at baseline, 37 (32–51) mL/min/1.73 m^2 for CKD progressors and 44 (34–61) mL/min/1.73 m^2 for those without CKD progression (p = 0.003); the median urine protein creatinine ratio (uPCR) was 0.038 (0.016–0.82) g/mmol for CKD progressors and 0.016 (0.008–0.032) g/mmol for those without CKD progression (p = 0.001); median haemoglobin of 13.1 (11.7–14.4) g/dl for CKD progressors and 13.7 (12.2–15.3) g/dl for those without CKD progression, p = 0.023 (Table 1).

Prevalence of CKD progression, CKD remission and CKD regression. During the 2 years of follow up, a total of 147 (49.5%) patients had progression of CKD whereby 35.0% changed to a more advanced stage of CKD, 19.9% had greater than 30% reduction of eGFR in two years and 48.5% had a sustained decline in eGFR of $>$ 4 ml/min/1.73 m^2/year. A total of 98 (33%) patients were observed to have remission of CKD, while 52 (17.5%) patients had CKD regression (Fig 1A and 1B).

Clinical profile of black patients who had CKD progression. Of the 147 black patients who had CKD progression, the majority (95.2%) of patients had hypertension, 59 (40.1%) patients had diabetes mellitus and 58 (39.5%) had both hypertension and diabetes mellitus.

Table 1. Baseline demographic and clinical characteristics of CKD progressors and non-progressors.

Characteristic	CKD progression (n = 147)	No CKD progression (n = 150)	P-value
	Proportion (%) or Median (IQR)	Proportion (%) or Median (IQR)	
Age (years)	58 (46–67)	57 (45–66)	0.355
Sex			
Male	82 (55.78%)	74 (49.33%)	
Female	65 (44.22%)	76 (50.67%)	0.266
Marital status			
Single	39 (26.53%)	50 (33.33%)	
Married	81 (55.10%)	73 (48.67%)	
Widow/Widower	18 (12.24%)	19 (12.67%)	
Separated/Divorced	9 (6.12%)	8 (5.33%)	0.608
Highest level of education			
No formal education	18 (12.24%)	16 (10.67%)	
Primary	31 (21.09%)	36 (24.00%)	
Secondary	52 (35.37%)	43 (28.67%)	
Tertiary	46 (31.29%)	55 (36.67%)	0.549
Occupation			
Unemployed	23 (15.65%)	21 (14.00%)	
Domestic workers	25 (17.01%)	31 (20.67%)	
Self employed	33 (22.45%)	32 (21.33%)	
Public / Private servant	54 (36.73%)	53 (35.33%)	
Retired	12 (8.16%)	13 (8.67%)	0.943
BMI (kg/m^2)	30.6 (26.84–35.67)	29.39 (25.97–33.4)	0.193
SBP (mmHg)	140 (132–140)	140 (126–140)	0.088
DBP (mmHg)	83 (74–90)	82 (73–90)	0.319
uPCR (g/mmol)	0.038 (0.016–0.82)	0.016 (0.008–0.032)	**0.001**
Creatinine (umol/L)	148 (118–183)	134 (104–161)	**0.002**
eGFR ($ml/min/1.72m^2$)	37 (32–51)	44 (34–61)	**0.003**
FBG (mmol/L)	4.5 (4.2–5.4)	4.4 (4.2–4.9)	0.187
HbA1C (%)	7.0 (7.0–7.0)	7.0 (6.6–7.0)	0.184
Haemoglobin (g/dl)	13.1 (11.7–14.4)	13.7 (12.2–15.3)	**0.023**
Transferrin (g/L)	2.49 (2.25–2.78)	2.59 (2.29–2.85)	0.782
WBC (x 10^9 cells/L)	6.1 (5.06–7.84)	6.46 (4.81–7.74)	0.549
Platelets (x 10^9 cells/L)	251 (211–320)	269 (218–323)	**0.017**
Uric acid (mmol/L)	0.42 (0.35–0.51)	0.40 (0.31–0.48)	**0.010**
HDL cholesterol (mmol /L)	1.16 (0.99–1.43)	1.25 (1.01–1.56)	0.114
Calcium (mmol /L)	2.30 (2.23–2.40)	2.34 (2.25–2.42)	0.095
Phosphate (mmol /L)	1.11 (0.93–1.26)	1.02 (0.88–1.16)	**0.022**
Sodium (mmol/L)	141 (139–143)	141 (138–143)	0.849
Potassium (mmol/L)	4.3 (4.0–4.7)	4.2 (3.8–4.5)	0.068
Bicarbonate (mol/L)	22 (20–24)	22 (20–24)	0.871

IQR, interquartile range; uPCR, urine protein creatinine ratio; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood sugar; HbA1C, glycosylated hemoglobin A1C; WBC, white blood cells; HDL, high density lipoprotein; SBP, systolic blood pressure.

https://doi.org/10.1371/journal.pone.0276356.t001

About half (48.3%) of the CKD progressors presented with severely increased proteinuria as compared to 30 (20.0%) of those without CKD progression. Anaemia was noted in 67 (45.6%) patients with CKD progression and in 40 (26.7%) patients in those without CKD progression. Low serum calcium levels were noted in 26 (17.7%) of those with CKD progression and in 10

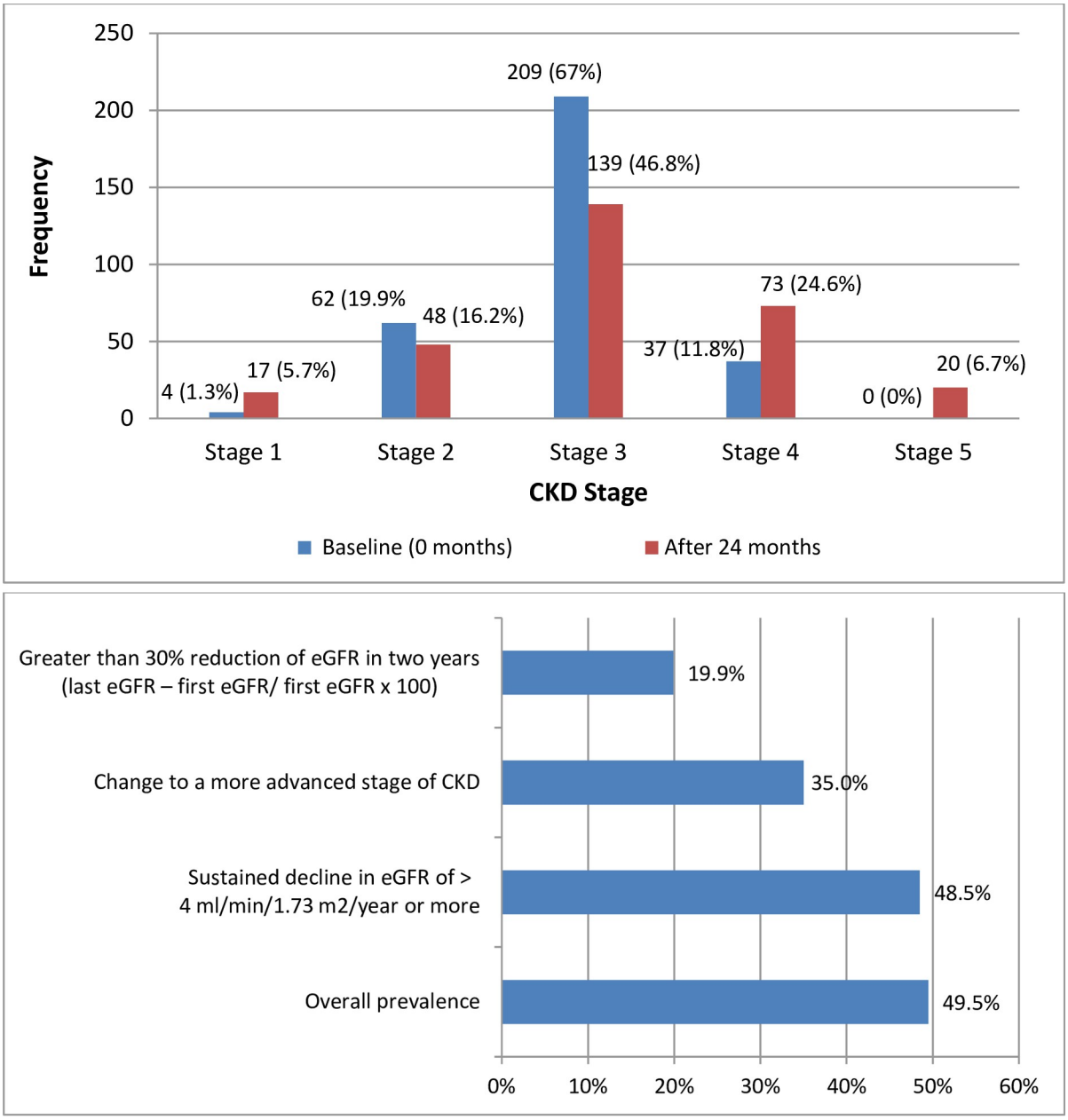

Fig 1. a: CKD stages at baseline and at 24 months follow up; b: Estimation of CKD progression using different eGFR criteria.

https://doi.org/10.1371/journal.pone.0276356.g001

(6.7%) patients of those without CKD progression, while high serum phosphate levels were noted in 18 (12.3%) patients in those with CKD progression and in 6 (4.0%) patients of those without CKD progression. Low serum sodium levels were noted in 12 (8.2%) of those with CKD progression and in 3 (2.0%) of patients without CKD progression, while high serum potassium levels were noted in 21 (14.3%) patients who had CKD progression and in 7 (4.7%) of patients without CKD progression. Hyperuricemia was present in 50 (34.0%) patients with CKD progression as compared to 24 (16.0%) patients without CKD progression. Majority (76.9%) patients with CKD progression were using more than 4 anti-hypertensives for their blood pressure control as compared to 57.3% in those patients without CKD progression. For

patients with CKD progression, the majority (85.7%) of patients were on calcium channel blockers, 62.6% were on diuretics, 57.1% were on statins, 55.1% were on beta blockers, 31.3% were on insulin, 29.3% and were on aspirin. A total of 35 (23.8%) CKD progressors were on ACEs/ARBs compared with 25 (16.7%) non-progressors; there was no significant difference in CKD progression associated with the use of ACEIs/ARBs (Table 2).

Predictors of CKD progression. We divided the patients into two subgroups according to their CKD progression status after 2 years of follow up: CKD progression vs. no CKD progression. A total of 30 potential variables were identified after performing univariate logistic regression analyses. Backward elimination reduced this to 21 parameters; the factors associated with CKD progression after adjusting for age and sex on multivariate logistic regression analysis included diabetes mellitus (OR 1.8, 95% CI 0.9–3.6, P = 0.047), increasing HbA1C (OR 1.8, 95% CI 1.2–2.8, P = 0.007), severely increased proteinuria (OR 32.3, 95% CI 2.8–368.6, P = 0.005), moderately increased proteinuria (OR 23.3, 95% CI 2.6–230.1, P = 0.007), hypocalcaemia (OR 3.8, 95% CI 1.0–14.8, P = 0.047), anaemia (OR 2.1, 95% CI 1.0–4.3, P = 0.048), hyponatraemia (OR 4.5, 95% CI 0.8–23.6, P = 0.042) and current smoking (OR 2.8, 95% CI 0.9–8.6, P = 0.049 (Table 3).

Discussion

Our study identified a higher prevalence of progression of CKD in a prospective longitudinal study of black patients with CKD attending the kidney outpatient clinic at CMJAH in Johannesburg compared to literature reports. We found a high prevalence of CKD progression with 49.5% of the study patients with CKD progression, which is a higher prevalence of progression than the reported prevalence of 46.7% in a UK cohort study and 38% in a study conducted in northern California in USA [31, 35]. The possible explanation could be differences in the study populations; in our study we enrolled only black patients; black patients tend to have more rapid CKD progression even in the early stages of CKD [36, 37]. Also, black patients due to racial/ethnic disparities are at higher risk of CKD progression and its related complications than other races [38, 39]. This study established that 33% patients had CKD remission and 17.5% patients had CKD regression, similar to findings from other studies from the UK [35, 40]. A sustained decline in eGFR of $>$ 4 ml/min/1.73 m^2/year or more was able to identify 48.5% patients who had CKD progression, including those with rapid CKD progression, similar to other studies [31, 35].

Hypertension was prevalent in the study cohort, occurring in 96.7% of the study cohort at baseline and in 95.2% of CKD progressors and in 91.3% of those without progression. Of the patients with CKD progression, the majority (95.2%) had hypertension, 40.1% had diabetes mellitus and 39.5% had both hypertension and diabetes mellitus. Studies have reported CKD progression to be associated with CKD etiology and hypertension [41, 42]. Both systolic and diastolic blood pressure were not significantly associated with CKD progression in this study, unlike findings from other studies where higher SBP and DBP levels were associated with CKD and had higher risks of CKD progression [43, 44]. This difference could be due to the high prevalence (above 90%) of hypertension in both groups and an entry criterion of controlled blood pressure. Smoking was reported in 9.5% of our study patients who had CKD progression, with a 2.8-fold increased risk for CKD progression; studies have reported that smoking is significantly associated with a higher risk of CKD and smoking is strongly associated with CKD progression [45, 46]. Obesity and HDL cholesterol were not significantly associated with CKD progression in this study unlike findings from other studies where patients who had obesity and/or hyperlipidaemia had higher rates of CKD progression [47, 48]. This difference could be due to the high prevalence of obesity/overweight in both progressor and non-progressor groups.

Table 2. Baseline clinical and laboratory parameters of CKD progressors and non-progressors.

Parameter	CKD progression (n = 147) Proportion (%)	No CKD progression (n = 150) Proportion (%)	P-value
Diagnoses encountered			
Hypertension	140 (95.24%)	137 (91.33%)	0.179
Diabetes mellitus	59 (40.14%)	39 (26.00%)	**0.010**
Hypertension & Diabetes mellitus	58 (39.46%)	38 (25.3%)	**0.009**
Adult polycystic kidney disease	7 (4.76%)	4 (2.67%)	0.339
Reflux nephropathy	2 (1.36%)	3 (2.00%)	0.668
Obstructive uropathy	1 (0.68%)	0 (0.0%)	0.312
Unknown	2 (1.36%)	8 (5.33%)	0.058
Current smoking			
Yes	14 (9.52%)	8 (5.33%)	
No	133 (90.48%)	142 (96.67%)	0.168
Current Alcohol			
Yes	14 (9.52%)	18 (12.00%)	
No	133 (90.48%)	132 (88.00%)	0.493
Cardiovascular Diseases			
None	99 (67.35%)	121 (80.67%)	
Angina	28 (19.05%)	22 (14.67%)	
Myocardial infarction	9 (6.12%)	2 (1.33%)	
Heart failure	5 (3.40%)	3 (2.00%)	
Stroke	6 (4.08%)	2 (1.33%)	**0.030**
Medications			
None	4 (2.72%)	5 (3.33%)	0.758
Diuretics	92 (62.59%)	61 (40.67%)	**0.001**
ACEIs / ARBs	35 (23.81%)	25 (16.67%)	0.125
Aldactone	7 (4.76%)	4 (2.67%)	0.339
CCBs	126 (85.71%)	112 (74.67%)	**0.017**
Statins	84 (57.14%)	67 (44.67%)	**0.032**
Oral hypoglycemics	15 (10.2%)	21(14.0 0%)	0.316
Insulin	46 (31.29%)	22 (14.67%)	**0.001**
Allopurinol	16 (10.88%)	18 (12.00%)	0.763
Junior ASA	43 (29.25%)	26 (17.33%)	**0.015**
Beta blockers	81 (55.10%)	61 (40.67%)	**0.013**
Aldomet	36 (24.49%)	33 (22.0%)	0.611
Hydralazine	11 (7.48%)	8 (5.33%)	0.449
Nitrates (ISMN/ISDN)	4 (2.72%)	3 (2.00%)	0.682
Doxazosin	68 (46.26%)	66 (44.00%)	0.696
Others	47 (31.97%)	52 (34.67%)	0.622
No. of antihypertensives per patient			
0	4 (2.72%)	6 (4.00%)	
1–3	30 (20.40%)	58 (38.67%)	
≥ 4	113 (76.88%)	86 (57.33%)	**0.002**
uPCR (g/mmol)			
Normal to mildly increased (<0.015)	23 (15.65%)	59 (39.33%)	
Moderately increased (0.015–0.05)	48 (32.65%)	59 (39.33%)	
Severely increased (> 0.050)	71 (48.30%)	30 (20.00%)	
Nephrotic syndrome (> 0.350)	5 (3.40%)	2 (1.33%)	**0.001**
WBC (x 10^9 cells/l)			

(*Continued*)

Table 2. (Continued)

Parameter	CKD progression (n = 147) Proportion (%)	No CKD progression (n = 150) Proportion (%)	P-value
Low (> 4)	5 (3.40%)	12 (8.00%)	
Normal (4–11)	139 (94.56%)	131 (87.33%)	
High (>11)	3 (2.04%)	7 (4.67%)	0.096
Haemoglobin (g/dl)			
Normal (> 12.0 or 13.0)	80 (54.42%)	110 (73.33%)	
Anemia (<12.0 or 13.0)	67 (45.58%)	40 (26.67%)	**0.001**
Transferrin (g/dl)			
Low (< 2.0)	26 (17.69%)	13 (8.67%)	
Normal (2.0–3.60)	117 (79.59%)	134 (89.33%)	
High (>3.60)	4 (2.72%)	3 (2.00%)	0.061
Platelets (x 10^9 cells/l)			
Low (> 150)	2 (1.36%)	3 (2.00%)	
Normal (150–450)	142 (96.60%)	141 (94.00%)	
High (>450)	3 (2.04%)	6 (4.00%)	0.643
Calcium (mmol /l)			
Low (< 2.15)	26 (17.69%)	10 (6.67%)	
Normal (2.15–2.45)	107 (72.79%)	118 (78.67%)	
High (>2.45)	14 (9.52%)	22 (14.67%)	**0.009**
Phosphate (mmol /l)			
Low (< 0.80)	7 (4.76%)	16 (10.67%)	
Normal (0.80–1.55)	122 (82.99%)	128 (85.33%)	
High (>1.55)	18 (12.25%)	6 (4.00%)	**0.019**
Uric acid (mmol/l)			
Normal (0.16/0.21–0.36/0.43)	97 (65.99%)	126 (84.00%)	
High (> 0.36 or 0.43)	50 (34.01%)	24 (16.00%)	**0.001**
HDL cholesterol (mmol /l)			
Low (< 1.04)	43 (29.25%)	35 (23.33%)	
Normal (1.04–1.17)	28 (19.05%)	25 (16.67%)	
High (>1.17)	76 (51.70%)	90 (60.00%)	0.343
Sodium (mmol/l)			
Low (< 136)	12 (8.16%)	3 (2.00%)	
Normal (136–145)	130 (88.44%)	138 (92.00%)	
High (>145)	5 (3.40%)	9 (6.00%)	**0.034**
Potassium (mmol/l)			
Low (< 3.5)	10 (6.80%)	11 (7.33%)	
Normal (3.5–5.1)	116 (78.91%)	132 (88.0%)	
High (> 5.1)	21 (14.29%)	7 (4.67%)	**0.018**
Bicarbonate (mmol/l)			
Low (< 23)	97 (65.99%)	85 (56.67%)	
Normal (23–29)	46 (31.29%)	63 (42.00%)	
High (> 29)	4 (2.72%)	2 (1.33%)	0.130

uPCR, urine protein creatinine ratio; eGFR, estimated glomerular filtration rate; CCBs, calcium channel blockers; ACEIs, angiotensin converting enzyme inhibitors; ARBs, Aldosterone receptors blockers.

https://doi.org/10.1371/journal.pone.0276356.t002

Table 3. Predictors of CKD progression.

Characteristic	No. of patients	UNIVARIATE		MULTIVARIATE	
		OR (95% CI)	P. value	OR (95% CI)	P. value
Marital status					
Single	89	1(Reference)		1(Reference)	
Married	154	1.4 (0.8–2.4)	0.188	1.7 (0.8–3.7)	0.152
Widow/Widower	37	1.2 (0.6–2.6)	0.620	0.9 (0.3–2.9)	0.969
Separated/Divorced	17	1.4 (0.5–4.1)	0.490	1.4 (0.4–5.8)	0.605
Hypertension					
No	20	1(Reference)		1(Reference)	
Yes	277	1.8 (0.7–4.9)	0.186	0.2 (0.0–4.6)	0.343
Diabetes mellitus					
No	199	1(Reference)		1(Reference)	
Yes	98	1.9 (1.2–3.1)	0.010	1.8 (0.9–3.6)	**0.047**
Current smoking					
No	275	1(Reference)		1(Reference)	
Yes	22	1.8 (0.8–4.6)	0.174	2.8 (0.9–8.6)	**0.049**
BMI	297	1.0 (0.9–1.1)	0.189	1.0 (1.0–1.1)	0.609
SBP (mm hg)	297	1.0 (0.9–1.0)	0.135	1.0 (0.9–1.1)	0.700
DBP (mm hg)	297	1.0 (0.9–1.1)	0.142	1.0 (0.9–1.1)	0.908
HbA1C (%)	98	1.5 (1.2–2.0)	0.002	1.8 (1.2–2.8)	**0.007**
Cardiovascular Disease:					
None	220	1(Reference)		1(Reference)	
Angina	50	1.6 (0.8–2.8)	0.161	1.5 (0.6–3.7)	0.399
Myocardial infarction	11	5.5 (1.2–26.0)	0.032	3.8 (0.6–23.4)	0.151
Heart failure	8	2.0 (0.5–8.7)	0.338	1.4 (0.3–6.9)	0.710
Stroke	8	7.3 (0.9–61.9)	0.067	4.3 (0.4–42.3)	0.216
Proteinuria (g/mmol)					
Normal to mildly increased (<0.015)	82	1(Reference)		1(Reference)	
Moderately increased (0.015–0.05)	107	2.1 (1.1–3.9)	0.019	23.3 (2.4–230.1)	**0.007**
Severely increased (> 0.050)	101	6.1 (3.2–11.6)	0.000	32.3 (2.8–368.6)	**0.005**
Nephrotic syndrome (> 0.350)	7	6.4 (1.2–35.4)	0.033	3.1 (0.0–547.7)	0.665
Anaemia					
No	190	1(Reference)		1(Reference)	
Yes	107	2.3 (1.4–3.7)	0.001	2.1 (1.0–4.3)	**0.048**
Transferrin g/dl)					
Normal (2.0–3.60)	251	1(Reference)		1(Reference)	
Low (< 2.0)	39	2.3 (1.1–4.7)	0.022	1.1 (0.4–3.0)	0.858
High (>3.60)	7	1.5 (0.3–7.0)	0.584	0.9 (0.1–5.9)	0.883
WBC (x 10^9 cells/l)					
Normal (4–11)	270	1(Reference)		1(Reference)	
Low (> 4)	17	0.4 (0.1–1.2)	0.087	0.6 (0.1–2.4)	0.460
High (>11)	10	0.4 (0.1–1.6)	0.196	0.3 (0.0–2.1)	0.215
Calcium (mmol /l)					
Normal (2.15–2.45)	225	1(Reference)		1(Reference)	
Low (< 2.15)	36	2.9 (1.3–6.2)	0.008	3.8 (1.0–14.8)	**0.047**
High (>2.45)	36	0.7 (0.3–1.4)	0.335	0.9 (0.4–2.1)	0.809
Phosphate (mmol /l)					
Normal (0.80–1.55)	250	1(Reference)		1(Reference)	

(*Continued*)

Table 3. (Continued)

Characteristic	No. of patients	UNIVARIATE		MULTIVARIATE	
		OR (95% CI)	P. value	OR (95% CI)	P. value
Low (< 0.80)	23	0.5 (0.2–1.2)	0.098	0.7 (0.2–2.3)	0.567
High (>1.55)	24	3.0 (1.1–7.8)	0.027	2.0 (0.5–8.1)	0.315
Hyperuricaemia					
No	223	1(Reference)		1(Reference)	
YES	74	2.7 (1.6–4.7)	0.001	1.6 (0.8–3.5)	0.202
HDL cholesterol (mmol /l)					
Normal (1.04–1.17)	53	1(Reference)		1(Reference)	
Low (< 1.04)	78	0.8 (0.4–1.6)	0.468	0.7 (0.3–1.5)	0.333
High (>1.17)	166	0.5 (0.3–1.0)	0.051	0.6 (0.3–1.2)	0.154
Sodium (mmol/l)					
Normal (136–145)	268	1(Reference)		1(Reference)	
Low (< 136)	15	4.3 (1.2–15.4)	0.028	4.5 (0.8–23.6)	**0.042**
High (>145)	14	0.6 (0.2–1.8)	0.355	0.5 (1.1–2.2)	0.349
Potassium (mmol/l)					
Normal (3.5–5.1)	248	1(Reference)		1(Reference)	
Low (< 3.5)	21	1.0 (0.4–2.3)	0.941	0.9 (0.3–2.5)	0.958
High (> 5.1)	28	3.4 (1.4–8.3)	0.007	1.8 (0.7–5.1)	0.200
Bicarbonate (mmol/l)					
Normal (23–29)	109	1(Reference)		1(Reference)	
Low (< 23)	182	1.5 (1.0–2.5)	0.068	0.9 (0.4–1.8)	0.706
High (> 29)	6	2.7 (0.5–15.6)	0.256	7.3 (0.5–100.1)	0.135

P < 0.05 was used to identify potential variables, those with P <0.2 in univariate analysis were included in the multivariate analysis while adjusting for age and sex.

https://doi.org/10.1371/journal.pone.0276356.t003

Diabetes mellitus had a 1.8-fold increased risk for CKD progression and increased HbA1c levels had a 1.8-fold increased risk for CKD progression similar to findings from other studies where increased HbA1c levels was associated with CKD progression in patients with T2DM [49, 50]. Most (48.3%) patients with CKD progression presented with severely increased proteinuria; CKD progression was 32.3 times higher if a patient had severely increased proteinuria and 23.3 times higher if a patient had moderately increased proteinuria; studies have reported CKD progression to be increased in patients who present with higher levels of proteinuria [51, 52]. ACEIs or ARBs have shown to reduce proteinuria more effectively than other antihypertensives; in this study, few (20.2%) patients were using ACEIs or ARBs, similar to other studies reporting underutilization of ACEIs/ARBs in CKD patients [53, 54]. Emphasizing the critical need for nephrologists and clinicians to optimize safe and effective use of ACEIs/ARBs for RAAS blockade among CKD patients towards reducing proteinuria and slowing CKD progression [55, 56].

Anaemia was reported in 45.6% of patients who had CKD progression and was 2.1-fold increased with CKD progression and CKD was more severe if a patient had anaemia. Studies have reported that anaemia in CKD mainly results from impaired production of erythropoietin by the failing kidneys and anaemia is significantly associated with increased odds for CKD, CKD progression and worse clinical outcomes [57, 58]. Hyperuricaemia was significantly associated with CKD progression on univariate analysis in our study but this significance was lost on multivariate analysis; studies have reported that high serum uric acid levels commonly occur as a result of the impaired glomerular filtration rate (GFR) that occurs in CKD. Hyperuricaemia can also precede the development of CKD, predict incident CKD and is associated

with high risk for advanced CKD/ CKD progression [59, 60]. Hypocalcaemia was reported in 17.7% patients who had CKD progression with 3.8-fold association with CKD progression; low serum calcium levels are commonly caused by increased serum phosphorus and decreased renal production of 1,25(OH)2 vitamin D due to hyperparathyroidism. Hypocalcaemia is independently associated with CKD, and it tends to predict rapid CKD progression and severe CKD [61, 62]. Hyperphosphataemia was significantly associated with CKD progression on univariate analysis but this significance was lost on multivariate analysis; studies have reported that high serum phosphate levels predicted higher rates of CKD progression [63, 64].

Hyponatraemia was reported in 8.16% of those patients who had CKD progression; CKD progression was 4.5 times more common if a patient had low serum sodium levels. The kidneys have the ability to modulate sodium and water excretion, and CKD is frequently complicated with hyponatraemia probably due to fluid overload or diuretic usage. Hyponatraemia in CKD is associated with a higher risk of CKD progression, cardiovascular events, hospitalization and increased mortality [65, 66]. Hyperkalaemia was significantly associated with CKD progression on univariate analysis but this significance was lost on multivariate analysis. Studies have reported that high serum potassium levels are common in patients with chronic CKD and it is associated with decreased renal function and CKD progression; its prevalence increases as the eGFR declines [67, 68]. Metabolic acidosis was not significantly associated with CKD progression in this study; studies from other settings reported that patients with low serum bicarbonate levels had higher rates of CKD progression and an accelerated reduction in eGFR with poor outcomes [69, 70]. This difference could be due to the high prevalence of metabolic acidosis in both groups.

Conclusion

Our study identified a higher prevalence of CKD progression in a prospective longitudinal study of black patients with CKD compared with literature reports. CKD Progression was associated with proteinuria, diabetes mellitus, elevated HbA1c, anaemia, hypocalcaemia, hyponatraemia and current smoking in a cohort of black patients with CKD who had controlled hypertension and diabetes mellitus at baseline. These patients are at relatively high risk for CKD progression calling for nephrologists and clinicians to be vigilant in identifying black patients with CKD who are at risk of early CKD progression as this would allow risk stratification to improve their kidney disease outcomes. A sustained decline in eGFR of >4 ml/min/ 1.73 m^2/year identified the highest number of patients with CKD progression, and this may help nephrologists and clinicians to identify those progressors in addition to capturing those patients with rapid CKD progression who require more frequent monitoring, closer surveillance and management towards halting their CKD progression.

Acknowledgments

Special thanks to all patients attending the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) KOPD clinic for their willingness to participate in this study and to the staff at the CMJAH KOPD clinic and laboratory for their continued care, proper keeping of patient data and support which made this study possible. I thank the International Society of Nephrology (ISN), the University of the Witwatersrand, the University of Dodoma and Shinei industries (Aichi, Japan) Co. Ltd, for support, and providing a good and conducive environment for my training.

Author Contributions

Conceptualization: Alfred Meremo, Graham Paget, Raquel Duarte, Saraladevi Naicker.

Data curation: Alfred Meremo, Graham Paget, Raquel Duarte, Deogratius Bintabara, Saraladevi Naicker.

Formal analysis: Alfred Meremo, Deogratius Bintabara, Saraladevi Naicker.

Funding acquisition: Alfred Meremo, Raquel Duarte, Saraladevi Naicker.

Investigation: Alfred Meremo, Graham Paget, Raquel Duarte, Saraladevi Naicker.

Methodology: Alfred Meremo, Graham Paget, Raquel Duarte, Deogratius Bintabara, Saraladevi Naicker.

Project administration: Alfred Meremo, Graham Paget, Raquel Duarte, Saraladevi Naicker.

Resources: Alfred Meremo, Raquel Duarte, Deogratius Bintabara, Saraladevi Naicker.

Software: Alfred Meremo, Deogratius Bintabara, Saraladevi Naicker.

Supervision: Alfred Meremo, Graham Paget, Raquel Duarte, Saraladevi Naicker.

Validation: Alfred Meremo, Graham Paget, Deogratius Bintabara, Saraladevi Naicker.

Visualization: Alfred Meremo, Raquel Duarte, Deogratius Bintabara, Saraladevi Naicker.

Writing – original draft: Alfred Meremo, Raquel Duarte, Saraladevi Naicker.

Writing – review & editing: Alfred Meremo, Graham Paget, Raquel Duarte, Deogratius Bintabara, Saraladevi Naicker.

References

1. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020; 395(10225):709–33. https://doi.org/10.1016/S0140-6736(20)30045-3 PMID: 32061315
2. Fletcher BR, Damery S, Aiyegbusi OL, Anderson N, Calvert M, Cockwell P, et al. Symptom burden and health-related quality of life in chronic kidney disease: A global systematic review and meta-analysis. PLoS medicine. 2022; 19(4):e1003954. https://doi.org/10.1371/journal.pmed.1003954 PMID: 35385471
3. Ke C, Liang J, Liu M, Liu S, Wang C. Burden of chronic kidney disease and its risk-attributable burden in 137 low-and middle-income countries, 1990–2019: results from the global burden of disease study 2019. BMC Nephrology. 2022; 23(1):17. https://doi.org/10.1186/s12882-021-02597-3 PMID: 34986789
4. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease. Advances in experimental medicine and biology. 2019; 1165:3–15. https://doi.org/10.1007/978-981-13-8871-2_1 PMID: 31399958
5. Oluyombo R, Banjo Oguntade H, Soje M, Obajolowo O, Karim M. Obesity and CKD in Sub-Saharan Africa: A Narrative Review. Kidney Medicine. 2022; 4(2):100403. https://doi.org/10.1016/j.xkme.2021.11.001 PMID: 35243313
6. Laster M, Shen JI, Norris KC. Kidney Disease Among African Americans: A Population Perspective. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2018; 72(5 Suppl 1):S3–s7. https://doi.org/10.1053/j.ajkd.2018.06.021 PMID: 30343720
7. Umeukeje EM, Young BA. Genetics and ESKD Disparities in African Americans. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2019; 74(6):811–21. https://doi.org/10.1053/j.ajkd.2019.06.006 PMID: 31606237
8. Mathur R, Dreyer G, Yaqoob MM, Hull SA. Ethnic differences in the progression of chronic kidney disease and risk of death in a UK diabetic population: an observational cohort study. BMJ Open. 2018; 8(3):e020145. https://doi.org/10.1136/bmjopen-2017-020145 PMID: 29593020
9. Bukabau JB, Sumaili EK, Cavalier E, Pottel H, Kifakiou B, Nkodila A, et al. Performance of glomerular filtration rate estimation equations in Congolese healthy adults: The inopportunity of the ethnic correction. PloS one. 2018; 13(3):e0193384. https://doi.org/10.1371/journal.pone.0193384 PMID: 29499039

10. Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. BMC nephrology. 2018; 19(1):125. https://doi.org/10.1186/s12882-018-0930-5 PMID: 29859046

11. Abd ElHafeez S, Bolignano D, D'Arrigo G, Dounousi E, Tripepi G, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. BMJ Open. 2018; 8(1):e015069. https://doi.org/10.1136/bmjopen-2016-015069 PMID: 29326180

12. Thurlow JS, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, et al. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy. American Journal of Nephrology. 2021; 52(2):98–107. https://doi.org/10.1159/000514550 PMID: 33752206

13. Jardine MJ, Kasiske B, Adu D, Alrukhaimi M, Ashuntantang GE, Basnet S, et al. Closing the gap between evidence and practice in chronic kidney disease. Kidney International Supplements. 2017; 7 (2):114–21. https://doi.org/10.1016/j.kisu.2017.07.006 PMID: 30675425

14. Adeniyi AB, Davids MR, Laurence CE, Volmink JA. Prevalence of chronic kidney disease and association with cardiovascular risk factors among teachers in Cape Town, South Africa. Clinical Kidney Journal. 2017; 10(3):363–9. https://doi.org/10.1093/ckj/sfw138 PMID: 28621342

15. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nature reviews Nephrology. 2020; 16(5):269–88. https://doi.org/10.1038/s41581-019-0248-y PMID: 32060481

16. Cortinovis M, Perico N, Ruggenenti P, Remuzzi A, Remuzzi G. Glomerular hyperfiltration. Nature reviews Nephrology. 2022.

17. Cortinovis M, Ruggenenti P, Remuzzi G. Progression, Remission and Regression of Chronic Renal Diseases. Nephron. 2016; 134(1):20–4. https://doi.org/10.1159/000445844 PMID: 27096936

18. Liu P, Quinn RR, Lam NN, Al-Wahsh H, Sood MM, Tangri N, et al. Progression and Regression of Chronic Kidney Disease by Age Among Adults in a Population-Based Cohort in Alberta, Canada. JAMA network open. 2021; 4(6):e2112828.

19. Brück K, Jager KJ, Zoccali C, Bello AK, Minutolo R, Ioannou K, et al. Different rates of progression and mortality in patients with chronic kidney disease at outpatient nephrology clinics across Europe. Kidney International. 2018; 93(6):1432–41. https://doi.org/10.1016/j.kint.2018.01.008 PMID: 29656901

20. Levin A. Improving Global Kidney Health: International Society of Nephrology Initiatives and the Global Kidney Health Atlas. Annals of Nutrition and Metabolism. 2018; 72(suppl 2)(2):28–32. https://doi.org/10.1159/000488123 PMID: 29925068

21. Zhang J, Healy HG, Venuthurupalli SK, Tan KS, Wang Z, Cameron A, et al. Blood pressure management in hypertensive people with non-dialysis chronic kidney disease in Queensland, Australia. BMC Nephrol. 2019; 20(1):348. https://doi.org/10.1186/s12882-019-1532-6 PMID: 31484506

22. Kuo IC, Lin HY, Niu SW, Lee JJ, Chiu YW, Hung CC, et al. Anemia modifies the prognostic value of glycated hemoglobin in patients with diabetic chronic kidney disease. PloS one. 2018; 13(6):e0199378. https://doi.org/10.1371/journal.pone.0199378 PMID: 29933406

23. Nelson ML, Buchanan-Peart KR, Oribhabor GI, Khokale RV, Cancarevic I. Survival of the Fittest: Addressing the Disparities in the Burden of Chronic Kidney Disease. Cureus. 2020; 12(7):e9499. https://doi.org/10.7759/cureus.9499 PMID: 32879822

24. Chu CD, Powe NR, McCulloch CE, Crews DC, Han Y, Bragg-Gresham JL, et al. Trends in Chronic Kidney Disease Care in the US by Race and Ethnicity, 2012–2019. JAMA network open. 2021; 4(9): e2127014. https://doi.org/10.1001/jamanetworkopen.2021.27014 PMID: 34570204

25. Jose AP, Awasthi A, Kondal D, Kapoor M, Roy A, Prabhakaran D. Impact of repeated blood pressure measurement on blood pressure categorization in a population-based study from India. Journal of human hypertension. 2019; 33(8):594–601. https://doi.org/10.1038/s41371-019-0200-4 PMID: 30979950

26. Research NS. Health Survey for England 2016: adult health trends. Health and Social Care Information Centre London; 2017.

27. Babitt JL, Eisenga MF, Haase VH, Kshirsagar AV, Levin A, Locatelli F, et al. Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney international. 2021; 99(6):1280–95. https://doi.org/10.1016/j.kint.2021.03.020 PMID: 33839163

28. Tsai JW, Cerdeña JP, Goedel WC, Asch WS, Grubbs V, Mendu ML, et al. Evaluating the Impact and Rationale of Race-Specific Estimations of Kidney Function: Estimations from U.S. NHANES, 2015–2018. EClinicalMedicine. 2021; 42:101197. https://doi.org/10.1016/j.eclinm.2021.101197 PMID: 34849475

29. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney Disease, Race, and GFR Estimation. Clinical journal of the American Society of Nephrology: CJASN. 2020; 15(8):1203–12.

30. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. Jama. 2014; 311(24):2518–31. https://doi.org/10.1001/jama.2014.6634 PMID: 24892770

31. Go AS, Yang J, Tan TC, Cabrera CS, Stefansson BV, Greasley PJ, et al. Contemporary rates and predictors of fast progression of chronic kidney disease in adults with and without diabetes mellitus. BMC nephrology. 2018; 19(1):146. https://doi.org/10.1186/s12882-018-0942-1 PMID: 29929484

32. Rodríguez-Ortiz ME, Pontillo C, Rodríguez M, Zürbig P, Mischak H, Ortiz A. Novel Urinary Biomarkers For Improved Prediction Of Progressive Egfr Loss In Early Chronic Kidney Disease Stages And In High Risk Individuals Without Chronic Kidney Disease. Scientific reports. 2018; 8(1):15940. https://doi.org/10.1038/s41598-018-34386-8 PMID: 30374033

33. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of biomedical informatics. 2019; 95:103208. https://doi.org/10.1016/j.jbi.2019.103208 PMID: 31078660

34. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009; 42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010 PMID: 18929686

35. Ali I, Chinnadurai R, Ibrahim ST, Green D, Kalra PA. Predictive factors of rapid linear renal progression and mortality in patients with chronic kidney disease. BMC Nephrol. 2020; 21(1):345. https://doi.org/10.1186/s12882-020-01982-8 PMID: 32795261

36. Hounkpatin HO, Fraser SDS, Honney R, Dreyer G, Brettle A, Roderick PJ. Ethnic minority disparities in progression and mortality of pre-dialysis chronic kidney disease: a systematic scoping review. BMC Nephrology. 2020; 21(1):217. https://doi.org/10.1186/s12882-020-01852-3 PMID: 32517714

37. Diamantidis CJ, Zepel L, Wang V, Smith VA, Hudson Scholle S, Tamayo L, et al. Disparities in Chronic Kidney Disease Progression by Medicare Advantage Enrollees. American journal of nephrology. 2021; 52(12):949–57. https://doi.org/10.1159/000519758 PMID: 34875668

38. Clark-Cutaia MN, Rivera E, Iroegbu C, Squires A. Disparities in chronic kidney disease-the state of the evidence. Current opinion in nephrology and hypertension. 2021; 30(2):208–14. https://doi.org/10.1097/MNH.0000000000000688 PMID: 33464006

39. Bock F, Stewart TG, Robinson-Cohen C, Morse J, Kabagambe EK, Cavanaugh KL, et al. Racial disparities in end-stage renal disease in a high-risk population: the Southern Community Cohort Study. BMC Nephrology. 2019; 20(1):308. https://doi.org/10.1186/s12882-019-1502-z PMID: 31390993

40. Hirst JA, Taal MW, Fraser SD, Mena JMO, O'Callaghan CA, McManus RJ, et al. Change in glomerular filtration rate over time in the Oxford Renal Cohort Study: observational study. The British journal of general practice: the journal of the Royal College of General Practitioners. 2022; 72(717):e261–e8. https://doi.org/10.3399/BJGP.2021.0477 PMID: 34990394

41. Vesga JI, Cepeda E, Pardo CE, Paez S, Sanchez R, Sanabria RM. Chronic Kidney Disease Progression and Transition Probabilities in a Large Preventive Cohort in Colombia. International journal of nephrology. 2021; 2021:8866446. https://doi.org/10.1155/2021/8866446 PMID: 33868729

42. Fiseha T, Ahmed E, Chalie S, Gebreweld A. Prevalence and associated factors of impaired renal function and albuminuria among adult patients admitted to a hospital in Northeast Ethiopia. PloS one. 2021; 16(2):e0246509. https://doi.org/10.1371/journal.pone.0246509 PMID: 33539455

43. Lee JY, Park JT, Joo YS, Lee C, Yun HR, Yoo TH, et al. Association of Blood Pressure With the Progression of CKD: Findings From KNOW-CKD Study. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2021; 78(2):236–45. https://doi.org/10.1053/j.ajkd.2020.12.013 PMID: 33444666

44. Chang TI, Lim H, Park CH, Rhee CM, Moradi H, Kalantar-Zadeh K, et al. Associations of Systolic Blood Pressure With Incident CKD G3-G5: A Cohort Study of South Korean Adults. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2020; 76(2):224–32. https://doi.org/10.1053/j.ajkd.2020.01.013 PMID: 32305207

45. Lee S, Kang S, Joo YS, Lee C, Nam KH, Yun HR, et al. Smoking, Smoking Cessation, and Progression of Chronic Kidney Disease: Results From KNOW-CKD Study. Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco. 2021; 23(1):92–8. https://doi.org/10.1093/ntr/ntaa071 PMID: 32364601

46. Oliveira Coelho F, Andrade L. Smoking and Kidney Disease: Risk Factors, Challenges, and Preventive Strategies. Contributions to nephrology. 2021; 199:179–87. https://doi.org/10.1159/000517749 PMID: 34344004

47. Yun HR, Kim H, Park JT, Chang TI, Yoo TH, Kang SW, et al. Obesity, Metabolic Abnormality, and Progression of CKD. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2018; 72(3):400–10. https://doi.org/10.1053/j.ajkd.2018.02.362 PMID: 29728317

48. Strazzella A, Ossoli A, Calabresi L. High-Density Lipoproteins and the Kidney. Cells. 2021;10(4).

49. Khunti K, Charbonnel B, Chen H, Cherney DZ, Cooper A, Fenici P, et al. Prevalence and progression of chronic kidney disease among patients with type 2 diabetes: Insights from the DISCOVER study. Diabetes, obesity & metabolism. 2021; 23(8):1956–60. https://doi.org/10.1111/dom.14401 PMID: 33852196

50. Yasuno T, Maeda T, Tada K, Takahashi K, Ito K, Abe Y, et al. Effects of HbA1c on the Development and Progression of Chronic Kidney Disease in Elderly and Middle-Aged Japanese: Iki Epidemiological Study of Atherosclerosis and Chronic Kidney Disease (ISSA-CKD). Internal medicine (Tokyo, Japan). 2020; 59(2):175–80. https://doi.org/10.2169/internalmedicine.3242-19 PMID: 31554753

51. Qin X, Hu H, Cen J, Wang X, Wan Q, Wei Z. Association Between Urinary Protein-to-Creatinine Ratio and Chronic Kidney Disease Progression: A Secondary Analysis of a Prospective Cohort Study. Frontiers in medicine. 2022; 9:854300. https://doi.org/10.3389/fmed.2022.854300 PMID: 35433766

52. Buyadaa O, Magliano DJ, Salim A, Koye DN, Shaw JE. Risk of Rapid Kidney Function Decline, All-Cause Mortality, and Major Cardiovascular Events in Nonalbuminuric Chronic Kidney Disease in Type 2 Diabetes. Diabetes care. 2020; 43(1):122–9.

53. Bhandari S, Chadburn M. How Do We Navigate the Complexities Surrounding the Use of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers in Chronic Kidney Disease? Mayo Clinic Proceedings. 2019; 94(11):2166–9. https://doi.org/10.1016/j.mayocp.2019.09.014 PMID: 31685147

54. Leon SJ, Whitlock R, Rigatto C, Komenda P, Bohm C, Sucha E, et al. Hyperkalemia-Related Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in CKD: A Population-Based Cohort Study. American Journal of Kidney Diseases. https://doi.org/10.1053/j.ajkd.2022.01.002 PMID: 35085685

55. Burnier M. Renin-Angiotensin System Blockade in Advanced Kidney Disease: Stop or Continue? Kidney Med. 2020; 2(3):231–4. https://doi.org/10.1016/j.xkme.2020.04.002 PMID: 32734939

56. Loutradis C, Price A, Ferro CJ, Sarafidis P. Renin-angiotensin system blockade in patients with chronic kidney disease: benefits, problems in everyday clinical use, and open questions for advanced renal dysfunction. Journal of human hypertension. 2021; 35(6):499–509. https://doi.org/10.1038/s41371-021-00504-9 PMID: 33654237

57. Shaikh H, Aeddula NR. Anemia Of Chronic Renal Disease. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

58. Wittbrodt ET, James G, Kumar S, van Haalen H, Chen H, Sloand JA, et al. Contemporary outcomes of anemia in US patients with chronic kidney disease. Clinical kidney journal. 2022; 15(2):244–52. https://doi.org/10.1093/ckj/sfab195 PMID: 35145639

59. Sharma G, Dubey A, Nolkha N, Singh JA. Hyperuricemia, urate-lowering therapy, and kidney outcomes: a systematic review and meta-analysis. Therapeutic advances in musculoskeletal disease. 2021; 13:1759720x211016661. https://doi.org/10.1177/1759720X211016661 PMID: 34104231

60. Piani F, Sasai F, Bjornstad P, Borghi C, Yoshimura A, Sanchez-Lozada LG, et al. Hyperuricemia and chronic kidney disease: to treat or not to treat. Jornal brasileiro de nefrologia: 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia. 2021; 43(4):572–9. https://doi.org/10.1590/2175-8239-JBN-2020-U002 PMID: 33704350

61. Chang YP, Liao CM, Wang LH, Hu HH, Lin CM. Static and Dynamic Prediction of Chronic Renal Disease Progression Using Longitudinal Clinical Data from Taiwan's National Prevention Programs. Journal of clinical medicine. 2021; 10(14). https://doi.org/10.3390/jcm10143085 PMID: 34300251

62. Habas E, Sr., Eledrisi M, Khan F, Elzouki AY. Secondary Hyperparathyroidism in Chronic Kidney Disease: Pathophysiology and Management. Cureus. 2021; 13(7):e16388. https://doi.org/10.7759/cureus.16388 PMID: 34408941

63. Mendonça L, Gonçalves F, Sampaio S, Castro-Chaves P, Pereira L. Association between serum phosphorus and mortality in NHANES 2003–2006: the effect of gender and renal function. Journal of nephrology. 2022; 35(1):165–78. https://doi.org/10.1007/s40620-021-00969-4 PMID: 33580868

64. Molina P, Gavela E, Vizcaíno B, Huarte E, Carrero JJ. Optimizing Diet to Slow CKD Progression. Frontiers in medicine. 2021; 8:654250. https://doi.org/10.3389/fmed.2021.654250 PMID: 34249961

65. Arzhan S, Lew SQ, Ing TS, Tzamaloukas AH, Unruh ML. Dysnatremias in Chronic Kidney Disease: Pathophysiology, Manifestations, and Treatment. Frontiers in medicine. 2021; 8:769287. https://doi.org/10.3389/fmed.2021.769287 PMID: 34938749

66. Marroquin MV, Sy J, Kleine CE, Oveyssi J, Hsiung JT, Park C, et al. Association of pre-ESKD hyponatremia with post-ESKD outcomes among incident ESKD patients. Nephrology, dialysis, transplantation:

official publication of the European Dialysis and Transplant Association—European Renal Association. 2022; 37(2):358–65. https://doi.org/10.1093/ndt/gfab203 PMID: 34390572

67. Morales E, Cravedi P, Manrique J. Management of Chronic Hyperkalemia in Patients With Chronic Kidney Disease: An Old Problem With News Options. Front Med (Lausanne). 2021; 8:653634. https://doi.org/10.3389/fmed.2021.653634 PMID: 34150795

68. Watanabe R. Hyperkalemia in chronic kidney disease. Revista da Associacao Medica Brasileira (1992). 2020;66Suppl 1(Suppl 1):s31–s6.

69. Adamczak M, Surma S. Metabolic Acidosis in Patients with CKD: Epidemiology, Pathogenesis, and Treatment. Kidney diseases (Basel, Switzerland). 2021; 7(6):452–67. https://doi.org/10.1159/000516371 PMID: 34901192

70. Tangri N, Reaven NL, Funk SE, Ferguson TW, Collister D, Mathur V. Metabolic acidosis is associated with increased risk of adverse kidney outcomes and mortality in patients with non-dialysis dependent chronic kidney disease: an observational cohort study. BMC nephrology. 2021; 22(1):185. https://doi.org/10.1186/s12882-021-02385-z PMID: 34011303