Kidney and Blood Pressure Research

Kidney Blood Press Res , DOI: 10.1159/000533438
Received: February 24, 2023
Accepted: August 3, 2023
Published online: August 5, 2023

Systolic blood pressure and the risk of kidney replacement therapy and mortality in patients with chronic kidney disease stage 4-5

Chávez-Iñiguez JS, Zaragoza JJ, Camacho- Guerrero JR, Villavicencio-Cerón V, Valdez-Ortiz R, Huerta-Orozco AE, Chávez-Alonso G, Oliva-Martinez AE, Díaz-Villavicencio B, Calderón-García CE, González-Barajas JD, Arizaga-Nápoles M, De La Vega-Méndez FM, Gómez-Fregoso JA, Rodríguez-García FG, Navarro-Blackaller G, Medina-González R, Alcantar-Vallin L, García-García G

ISSN: 1420-4096 (Print), eISSN: 1423-0143 (Online)
https://www.karger.com/KBR
Kidney and Blood Pressure Research

Systolic blood pressure and the risk of kidney replacement therapy and mortality in patients with chronic kidney disease stage 4-5

Jonathan S. Chávez-Iñiguez [1,2], Jose J. Zaragoza [3], Jahir R. Camacho- Guerrero [1,2], Vanessa Villavicencio-Cerón [4], Rafael Valdez-Ortiz [5], Ana E. Huerta-Orozco [1,2], Gael Chávez-Alonso [2], Ana E. Oliva-Martinez[1,2], Bladimir Díaz-Villavicencio[1,2], Clementina E. Calderón-García[1,2], Jose D. González-Barajas[1,2], Manuel Arizaga-Nápoles[1,2], Frida M. De La Vega-Méndez[1,2], Juan A. Gómez-Fregoso[1], Francisco G. Rodríguez-García [1], Guillermo Navarro-Blackaller [1], Ramón Medina-González [1], Luz Alcantar-Vallin[1,2] and Guillermo García-García[2].

1 Nephrology Service, Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Jalisco. Mexico.
2 University of Guadalajara Health Sciences Center, Guadalajara, Jalisco. Mexico.
3 Master's and Doctorate Program in Medical, Dental and Health Sciences, National Autonomous University of Mexico
4 IESS (Ecuadorian Institute of Social Security) General Hospital Portoviejo of the Ecuatorian Institute of Nephrology. Villa Renal (institute of nephrology), Portoviejo, Manabí. Ecuador
5 Service of Nephrology, General Hospital of Mexico, Dr. Eduardo Liceaga, Mexico City, Mexico

Running head: Systolic blood pressure and outcomes in advanced chronic kidney disease

Corresponding author:
Jonathan S. Chávez-Íñiguez
Nephrology Service, Hospital Civil de Guadalajara Fray Antonio Alcalde, Hospital 278, Colonia Centro. C.P. 44150. Guadalajara, Jalisco. Mexico.
Phone: 0152 333942400 ext 49312
Email: jonarchi_10@hotmail.com
Twitter: @JonathanNefro
ORCID https://orcid.org/0000-0003-2786-6667
Number of Tables: 5
Number of Figures: 3
Word count:
Keywords: Hypertension, kidney replacement therapy, chronic kidney disease, mortality.

Abstract

Introduction

In patients with chronic kidney disease stage 4 and 5 (CKD stages 4-5) without dialysis and arterial hypertension, it is unknown if the values of systolic blood pressure (SBP) considered in control <120 mmHg are associated with kidney replacement therapy (KRT) and mortality.

Methods

In this retrospective cohort study, hypertensive CKD stages 4-5 patients attending the Renal Health Clinic at the Hospital Civil de Guadalajara were enrolled. We divided them into those that achieved SBP < 120 mmHg (controlled group) and those who did not (>120 mmHg), the uncontrolled group. Our primary objective was to analyze the association between the controlled group and KRT; the secondary objective was the mortality risk, and if there were subgroups of patients that achieved more benefit. Data were analyzed using Stata software, version. 15.1.

Results

During 2017 to 2022 a total 275 hypertensive CKD stages 4-5 patients met the inclusion criteria for the analysis, 62 in the controlled group and 213 in the uncontrolled group; mean age 61 years, 49.82% were male, SBP was significantly lower in the controlled group (111 mmHg) compared to the uncontrolled group (140 mmHg), eGFR was similar between groups (20.41 ml/min/1.73m^2). There was a tendency to increase the mortality risk in the uncontrolled group (HR 6.47 (0.78-53.27); p= 0.082) and an association by the Kaplan-Meir analysis (Log-rank p= 0.043). The subgroup analysis for risk of KRT in the controlled group revealed that patients ≥ 61 years had a lower risk of KRT (HR 0.87 (95% CI, 0-76-0.99); p=0.03, p of interaction = 0.005), but no differences were found in the subgroup analysis for mortality. In a follow-up of 1.34 years, no association was found in the risk of KRT according to the controlled or uncontrolled groups in a multivariate Cox analysis.

Conclusion

In a retrospective cohort of patients with CKD stages 4-5 and hypertension, SBP >120 mmHg was not associated with risk of KRT but could be associated with the risk of death. Clinical trials are required in this group of patients to demonstrate the impact of reaching the SBP goals recommended by the KDIGO guidelines.

Introduction

Approximately 850 million people have chronic kidney disease (CKD) worldwide, and more than 80% of them have hypertension [1]. The incidence of hypertension worsens as renal function decreases, increasing the risk of suffering from hypertension by 3.5 times when the glomerular filtration rate (GFR) is less than 30 ml/min/1.73 m^2 [2]. Hypertension is one of the largest contributors to the development of cardiovascular (CV) complications and worsening renal function. In a 5-year follow-up of patients with CKD stage 4, it was observed that 45% died, mostly due to CV events, this event being more common than starting dialysis [3]. Hypertension plays a fundamental role in CV death and is one of the largest contributors to mortality in CKD [4], which is why the nephrology community has for decades focused on lowering blood pressure (BP). It is believed that, by eliminating hypertension, we would observe the greatest reduction in CV death, and it would be more relevant than eliminating diabetes, obesity or smoking [5]. Although the criteria according to which BP is considered to be under control for people with CKD and hypertension have varied in recent decades, the KDIGO guidelines published in 2021 recommended a BP <120/80 mm Hg to consider control [6], justified mainly by the SPRINT clinical trial results [7]. Despite these recommendations, 69.5% of patients with CKD lack BP control [8]. However, major guideline bodies do not agree about BP targets for CKD [9]. Unfortunately, these major guideline discrepancies create an environment of uncertainty and directly affect the care of CKD patients, prompting intense debates and treatment changes that can impair quality of life and outcomes.

However, the appropriate treatment target for BP in advanced CKD populations (stage 4 and 5 without dialysis) remains unclear, and the benefits of intensive BP control are debated [10]. We believe that there is scarce evidence on the appropriate goals for systolic blood pressure (SBP) numbers to be achieved in patients with CKD G4-5 with hypertension, specifically to observe a benefit in outcomes such as kidney replacement therapy (KRT) and mortality. To contribute to shortening the existing gap in this area of interest, we conducted this study, in which we analyzed the association between SBP and the risk of KRT or death in patients with advanced CKD.

Materials and Methods

Study Design and Patient Population

A retrospective cohort study was conducted at the Hospital Civil de Guadalajara Fray Antonio Alcalde, Mexico, between August 2017 and June 2022; the hospital is a tertiary referral academic center with 964 beds. All patients considered were under the care of the nephrology service and attended the Renal Health Clinic, a interdisciplinary health care model that involves the participation of a nephrology nurse, a nutritionist, a psychologist, and a nephrologist. The clinic has the purpose of preventing the risks of renal and CV progression, optimizing the management of comorbidities, educating patients about KRT, and delaying the progression of CKD from a multiparametric and comprehensive perspective. For the purpose of this study we only included CKD stages 4 and 5 without dialysis patients with hypertension at baseline. CKD was defined by the KDIGO guidelines using the estimated glomerular filtration rate (eGFR) by the CKD-EPI equation less than 60 ml/min/1.73m^2 or any marker of kidney disease for more than 3 months. CKD stages 4 and 5 were defined as an eGFR of 29-15 ml/min/1.73 m^2 and ≤ 14 ml/min/1.73 m^2, respectively [11].

Hypertension under control was defined according to the 2021 KDIGO guidelines, in which controlled BP was defined as "treated with a target SBP of <120 mmHg, when tolerated, using standardized office BP measurement (2B)" [6], and SBP >120 mm Hg was considered uncontrolled. We decided to focus only on systolic pressure <120 mmHg because it is the current recommendation considered controlled by KDIGO [6].
We included patients >18 years old, CKD stages 4-5, who were not on dialysis or who had not undergone a kidney transplant, with a diagnosis of arterial hypertension or who were taking antihypertensives since their last visit; they had at least 3 follow-up visits during the study period, had a record of the BP during their visits, and had an eGFR record. Patients who did not meet any of the inclusion criteria were excluded. A nurse performed the BP measurements at the clinic using the OMRON HEM-907XL or HEM-6127 device, following the recommendations for CKD patients [12]. The most appropriate size for the 2 devices was chosen; the patients remained seated for at least 5 minutes, their arms were uncovered, speaking was not allowed during the measurements, 3 measurements were taken with a difference of 2-3 minutes between them, and the average of 3 readings obtained with 3 measurements to calculate the mean SBP and DBP for each participant was considered [13]; the results were commented upon and noted. The renal nutritionist focused on suggesting a low sodium diet (<2.4 g/day) in accordance with international recommendations [14], in addition to guiding food intake in accordance with the KDIGO guidelines for the management of CKD and hypertension [6] and increased physical activity [15]. Adherence to treatment was evaluated asking about the missing pills during the last month, by the nurse and again by the nephrologist. We considered adherence to be present when the doses were met on >80% of the days.

Our primary objective was to analyze whether there is an association between SBP considered Controlled, compared to Uncontrolled, and the start of KRT and, all-cause mortality as a secondary objective. Additionally, we considered whether there were subgroups of patients who achieved some benefit from reaching these SBP values. KRT was defined as the initiation of peritoneal dialysis, hemodialysis, or kidney transplantation. All-cause mortality was defined from the date of death from linked death certification records.
No financial compensation was provided. Written informed consent was obtained from participants. The study was approved by the Hospital Civil de Guadalajara Fray Antonio Alcalde Institutional Review Board (HCG/CEI-0550/15). This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [16].

Data Collection
Clinical characteristics, demographic information, and laboratory data were collected using automated retrieval from the institutional electronic medical records system. The main predictors of interest were KRT and all-cause mortality. Demographic and clinical variables were collected, including age, diabetes, BP, hypothyroidism, CKD stage, eGFR, smoking, cerebrovascular disease, ischemic heart disease, nephrotoxic drugs, and prespecified biochemical data, such as hemoglobin, cholesterol, serum albumin, proteinuria, platelets, leukocytes, glucose, urea, creatinine, sodium, potassium, chloride, phosphate, and calcium. Antihypertensive and other drugs were commonly prescribed. KRT consisted of hemodialysis or peritoneal dialysis. Indications for KRT were fluid overload resistant to diuretics, severe hyperkalemia, severe metabolic acidosis, and uremic manifestations, including encephalopathy, pericarditis, and seizures [17,18,19].

Statistical analysis
The incidence of KRT and all-cause death per 1000 person-years during follow-up was calculated. The distribution of the continuous variables was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests, with which their nonnormal distributions were confirmed. As a result, continuous variables were expressed as medians and interquartile ranges, while categorical variables were expressed as counts and proportions. Differences in categorical variables between the controlled and uncontrolled groups were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared with Wilcoxon's rank test.
The incidence of each outcome was expressed as the total number of events per 1000 patient-years at risk.
A Cox proportional hazards regression model was used to analyze the relationship between baseline BP and outcome variables. Initially, a univariate Cox analysis was performed with those variables with a $p < 0.20$ in the analysis of differences between groups of baseline characteristics. Subsequently, those that had $p < 0.20$ in the univariate

analysis were included in the Cox multivariate model to adjust the comparison for potential confounders. We used Kaplan-Meier plots to compare survival curves between SBP. In addition, Kaplan-Meier curves and log rank analyses were performed, separated by group (controlled and uncontrolled). Finally, a forest plot of the hazard ratio was performed by predefined subgroups to find those patients who obtained the greatest benefit from controlled SBP against the initiation of KRT and survival. Statistical significance was defined as $p < 0.05$. Data were analyzed using Stata software, version. 15.1 (StataCorp, College Station, TX, USA).

Results

During the period from 2017 to 2022, there were 11,250 consultations at the Renal Health Clinic for a total of 2,167 patients, of whom 1,892 were excluded for not meeting the inclusion criteria (22 for being <18 years old; 1,102 for having CKD stage 1, 2 or 3; 320 because of nonhypertensive; 12 for having a previous kidney transplant; 62 for having fewer than 3 consultations; and 374 for missing available SBP records or having <3 GFRe measurements). For the final analysis, a total of 275 patients were divided into 62 in the Controlled group and 213 in the Uncontrolled group, as shown in the flow chart of **Figure 1**.

Table 1 shows the baseline characteristics and the comparison between the patients in the Controlled and Uncontrolled SBP groups. No differences were found between the groups in age (61 years old) or in male sex (49.82%). As expected, SBP was significantly lower in the Controlled group (111 mm Hg) than in the Uncontrolled (140 mm Hg) group. In the same way, the DBP was 70 mm Hg compared to 80 mm Hg. The eGFR was similar between both groups, 20.41 ml/min/1.73 m^2, categorizing them as having CKD stage 4. In both groups the presence of diabetes and chronic heart failure was similar, 50% and 46% had it, respectively. No differences were found between the two groups in the mean concentrations of hemoglobin (11.6 g/dL), glucose (101 mg/dL), urea (104 mg/dL), serum albumin (4.0 g/dL) or electrolytes.

In the Controlled group, cholesterol levels were significantly lower (144.5 vs. 155.0 mg/dL), the patients had higher proteinuria (0 (0-0) vs. 0 (0-0.71); p=0.01), and they used more drugs, such as ACE inhibitors (45.16% vs. 28.64%) and omeprazole (6.45% vs. 1.42%). The Controlled group consumed fewer ß-blockers (11.29% vs. 26.29%) and calcium antagonists (24.19% vs. 41.78%). Other drugs, such as statins, furosemide, sodium bicarbonate, hypoglycemic agents, and insulin, were similar between the groups (p = >0.05 for all; **Table 1).**

SBP groups and the incidence of KRT and death

The median follow-up of the total cohort was 1.34 years (IQR 0.74–2.15), corresponding to 406.31 person-years. Regarding KRT, the median follow-up was 1.36 (0.74-2.17) years, corresponding to 388 person-years. There were 8 events in the controlled group and 26 events in the uncontrolled group, 34 in total, corresponding to a KRT incidence rate of 87.59 (IQR 62.58-12.59) per 1000 patient-year. In patients who died, the median follow-up was 1.36 years (IQR 0.74-2.24). One event was reported in the controlled group, and 14 events were reported in the uncontrolled group, corresponding to a total incidence rate of death of 36.97 (IQR 22.28-61.32) per 1000 patient-year. Details of the incidence rates of KRT and mortality can be seen in **Table 2**.

Primary Objective, KRT Risk by Controlled or Uncontrolled SPB Groups

Before propensity score matching, We evaluated the risk of KRT by SBP group. The univariate analysis included cholesterol, age, phosphate, eGFR, ß-blockers, omeprazole, proteinuria, ACE inhibitors, insulin, tamsulosin, calcium blockers, glucose, and ARB. The multivariate analysis included the Uncontrolled group, cholesterol, age, phosphate, eGFR, ß-blockers and omeprazole. We found that each 1-mg/dL increase in the cholesterol value greater than 200 mg/dL was associated with an increased risk of needing KRT (HR 1.01 (95% CI 1.00-1.02); p= 0.002), each year of age decreased the risk (HR 0.97 (95% CI 0.94-0.99); p=0.040), and as expected, each unit of eGFR greater than 20 ml/min/1.73m^2 decreased the risk (HR 0.93 (95% IQ 0.86-0.99); p=0.049). When evaluating the risk of KRT according to the SBP controlled or uncontrolled SBP groups in a multivariate Cox analysis, no association was found, nor was any association found in the Kaplan-Meier analysis curves, as shown in **Table 3** and **Supplemental Figure 1.**

Supplemental Table 1 shows the risks, and **Figure 2** shows the forest plot of the **subgroup analysis** for the **risk of needing KRT** among patients with controlled or uncontrolled SBP. In the Controlled group, people ≥61 years of age, compared to those <61, had a lower risk of needing KRT (HR 0.87 (95% CI 0-76-0.99); p=0.03, p of interaction = 0.005), and those patients with cholesterol <200 mg/dL presented a higher risk of needing KRT (HR 1.01 (95% CI 1.00-1.03);

p=0.02), but there was no significant interaction when compared to patients with cholesterol >200 mg/dL. There was no difference in risk in the other predefined subgroups.

Secondary objective of mortality risk by Controlled or Uncontrolled SPB groups

Using the same variables for the univariate analysis, cholesterol, Uncontrolled group, omeprazole, ACE inhibitors, age and ß-blockers, proteinuria, ARB, insulin, eGFR, glucose, calcium blockers and phosphate were included. No variables were associated with mortality risk. In the multivariate analysis, cholesterol, Uncontrolled SBP, omeprazole and ACEi were included. A tendency to increase the mortality risk was found in the Uncontrolled group (HR 6.47 (0.78-53.27); p = 0.082), and an association was found in the Kaplan Meir analysis and log rank test (**Table 4** and **Supplemental Figure 2**). Cholesterol and the use of ACE inhibitors were associated with an increased mortality risk (HR 1.01 (95% CI 1.00-1.02); p= 0.029 and HR 3.63 (95% CI 1.12-11.73), p=0.031, respectively) (**Table 4**).

Table 5 and **Figure 3** show the risks and the forest plot analysis of predefined **subgroups** for survival among patients with Controlled or Uncontrolled SBP, respectively, and no differences were found.

DISCUSSION

The key finding of the present analysis is that, in patients with CKD stages 4-5 with hypertension, we observed that SBP considered Uncontrolled (>120 mm Hg), compared to Controlled SBP (<120 mm Hg), was not associated with the risk of needing KRT, but could be associated with the risk of dying.

Our findings of the lack of benefit regarding KRT in CKD patients who maintain SBP levels considered controlled have been previously described. It is possible that the control of BP in these patients is not entirely beneficial for kidney function in the short- and medium-term follow-up. Three large clinical trials in CKD patients without diabetes MDRD [20], AASK [21] and REIN-2 [22] have aimed to achieve a BP <130/80 mm Hg, which is considered low, compared to <140/90 mm Hg. They failed to demonstrate kidney benefits. Neither reached even lower BP values (<120/80 mm Hg), as occurred in the SPRINT study and in our cohort. The SPRINT study randomized 9,361 patients (~2,600 with CKD stage 3) to intense control for BP <120 mm Hg compared to <140 mm Hg, and intense control had no difference in the risk of CKD progression [7].

Paradoxically, kidney function worsens in CKD patients randomized to intense BP control. In a post hoc study of the SPRINT trial that analyzed patients without CKD, it was observed that, among those who were randomized to intense control of SBP (<120 mm Hg), no improvement was noted in kidney function; in fact, this group had a greater probability of decreasing eGFR, with only 15.9 patients needing to be treated to cause 1 event of kidney function impairment [23]. In the subgroup of patients with CKD in the SPRINT study, the BP reached at 12 months in the intensive arm was 123.3/66.9 mm Hg, compared to 136.9/73.8 mm Hg; after a follow-up of 3.3 years, a 19% risk reduction in primary composite cardiovascular outcome and 28% reduction in risk of all-cause death were observed, but patients with SBP <120 mm Hg lost eGFR at a 47% faster rate [24].

A combined analysis of the AASK and MDRD studies described that, even 14 years after achieving BP control, no decrease in the risk of end-stage renal disease was observed [25]. A meta-analysis of 9 clinical trials and 8,127 patients with CKD did not demonstrate any kidney benefit of BP control [26]. In a Taiwanese cohort of 2,144 CKD stages 3-4 patients with diabetes who maintained an SBP between 96 mmHg and 110 mmHg, compared to 111 mmHg and 120 mmHg, the patients had a 3-14-fold increased risk of a kidney event [27]. The neutral or negative effect on eGFR in CKD patients who reach BP control is not well clarified. One explanation could be that, once they reach these BP goals, the risk of acute kidney injury increases by 51% [12], and the increased risk of postural hypotension [28]. Hypoperfusion affect the recovery of kidney regional blood flow and aggravated chronic inflammation and vasculopathy, accelerating kidney function loss [29].

The ESC/ESH guidelines in 2018 suggested treating hypertension according to age. In people with CKD and >80 years old, treatment should only be started before BP reaches >160/90 mm Hg [30]. In young people when BP reaches >140/90 mm Hg, but regardless of age, those with CKD suggested a goal of <139/79 mm Hg. Recently, in 2021, the ESC proposed starting the management of hypertension in CKD with a goal of 130-139 mm Hg [31].

A tendency to increase the mortality risk was found in the Uncontrolled group (>120). It has previously been described that uncontrolled hypertension is associated with a higher risk for CV morbidity and mortality [10], and reducing BP is beneficial.

In the CRIC cohort, 319 young patients (20 to 40 years old) with CKD stage 3a were observed over an 11-year follow-up, and those with SBP >130 mm Hg had a 2.3-fold increased risk of CV events or death and a 68% increased risk of CKD progression [32]. The SPRINT study was terminated prematurely due to the evident positive results since those assigned to the strict BP group (<120/80 mm Hg) had 19% fewer cardiovascular events and an 18% reduction in all causes of death [33]. Mortality benefits over SBP control (<130 mm Hg) in people with advanced CKD, such as stages3-5, were demonstrated in a meta-analysis of 18 clinical trials with 15,934 patients, in which this control was associated with a 14% decrease in the risk of death [34]. The largest clinical trials that have achieved systolic blood pressure figures <130 mm Hg, have used an average of 3 drugs to achieve this goal [35], so polypharmacy is frequent in these scenarios. The combination of antihypertensive drugs decreases the risk of death by 50% [36].
Achieving BP control in CKD patients is a clinical challenge and up to 30% of them are classified as resistant [37]. The pathophysiological mechanism of arterial hypertension in CKD is multifactorial and very complex. It is believed that it mainly involves marked endothelial dysfunction, increased renin production, decreased sodium excretion, and sympathetic hyperactivity [10].
Volume overload is a strong contributor to the development of hypertension in CKD G4-5 (38). In a cohort of patients with CKD stage 3b, it was observed that 43% had volume overload, and 23% of them were classified as having uncontrolled arterial hypertension [15]. It is important to mention that volume overload worsens as eGFR decreases. At the start of peritoneal dialysis, 56% had volume overload [39], and had positive relationships with BP, proteinuria, and pulse wave velocity and a negative correlation with eGFR [38].

Our findings on the association of high cholesterol values with mortality are similar to those reported in cohorts of patients with CKD stages 3-5. In one study, authors observed that total cholesterol >221 mg/dL was associated with a 2-fold increase in the risk of death over a follow-up of 2.8 years [40]. Advanced CKD patients exhibit lipid disorders that are more common than in the general population [41].
We found an association between the use of ACE inhibitors and mortality. Although it is an unexpected finding, it could have plausible explanations, including risk of hyperkalemia, hemodynamic alterations in kidney function and poor response to acute kidney injury events that can occur during this vulnerable period. The report of the NKF-KDOQI group in 2018 concluded that evidence for the use of renin angiotensin aldosterone system inhibitors (RAASi) is scarce in patients with advanced CKD [42]. The largest clinical trial on this topic is the STOP-ACEi study, in which patients with CKD stage 4 and an approximate BP of 136/76 mm Hg were randomized to continue with RAASi or discontinue them, and no differences were found between the groups in loss of kidney function, initiation of KRT or death [43]. To date, in these group of patients, the high-grade evidence is scarce.

SBP >120 mm Hg in patients with CKD stages 4-5 could represent a plausibly modifiable CV risk factor since could be related with an increased risk of death, consistent with the existing evidence in patients with normal kidney function or mildly reduced eGFR, but this association is not necessarily true for the risk of KRT. By reducing SBP to <120 mm Hg, as suggested in the KDIGO guidelines, we could prolong the lives of patients and allow them to better plan their KRT options, as well as improve how to carry out the transplant protocol [44] -- or in the worst of cases, to educate patients in a timely manner so that they can decide among PD [45], receiving an arteriovenous fistula for HD [46], or nondialysis treatments.

Our study has important limitations that must be considered when interpreting our results. The retrospective design of the study only allowed for finding associations and generating hypotheses. The lack of multiple variables could have affected the outcomes, albuminuria for example. The follow-up time was relatively short to assess KRT and mortality. Our analysis was based on eGFR using the CKD-EPI equation, which has inherent limitations and might not have been reliable during this critical process. We did not analyze patients who were lost to follow-up or who missed key information, such as not having ambulatory BP monitoring. The study was performed in a single center, which does not allow these results to be extrapolated to other races or ethnicities. The study represents real-world routine clinical practice, and thus, some variables were not routinely analyzed outside nephrology departments. The strengths of our cohort lie in having captured patients with advanced CKD, a group of patients poorly analyzed in previous studies. The patients were divided between SBP values according to the new recommendations of the KDIGO guidelines. Propensity score matching allowed us to homogenize the groups and perform a fairer comparison.

Conclusions

In a retrospective cohort of patients with stage 4-5 CKD and hypertension, SBP >120 mm Hg was not associated with the risk of needing KRT, although it could be associated with risk of death. Clinical trials are required in this group of patients to demonstrate the impact of reaching the SBP goals recommended by the KDIGO guidelines.

Acknowledgement: To all the Social Service students of medicine who have been in the nephrology service, without you these article would have been not possible.

Statement of Ethics The study was conducted in adherence with the Declaration of Helsinki and was approved by the Hospital Civil de Guadalajara Fray Antonio Alcalde Institutional Review Board (HCG/CEI-0550/15).

Consent to participate: written informed consent was obtained from participants

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding Sources: None of the authors received funding to conduct this study.

Authors' Contributions: Jonathan S. Chávez-Íñiguez and Jose J. Zaragoza designed the study, analyzed data, made tables, figures and wrote the manuscript. Ana E. Huerta-Orozco, Jahir R. Camacho- Guerrero, Vanessa Villavicencio-Cerón, Rafael Valdez-Ortiz, Gael Chávez-Alonso, Ana E. Oliva-Martinez, Bladimir Díaz-Villavicencio, Clementina E. Calderón-García, Jose D. González-Barajas, Manuel Arizaga-Nápoles, Frida M. De La Vega-Méndez, Juan A. Gómez-Fregoso, Francisco G. Rodríguez-García, Guillermo Navarro-Blackaller, Ramón Medina-González, Luz Alcantar-Vallin recolected data and wrote the manuscript. Guillermo García-García wrote the manuscript supervised all the process.

Data availability: The files and data are in the physical and electronic archive of the Civil Hospital of Guadalajara Fray Antonio Alcalde and can be requested with prior authorization. All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

REFERENCES

1. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019 Nov;96(5):1048-1050. doi: 10.1016/j.kint.2019.07.012. Epub 2019 Sep 30. PMID: 31582227.

2. Valdez Ortiz R, Escorza-Valdivia S, Benitez-Renteria S, Lopez-Alvarenga JC, Pérez-Navarro LM. Factors of Poor Prognosis Associated with Chronic Kidney Disease by Stage in Ambulatory Patients: A Cross-sectional Study. Arch Med Res. 2022 Jul;53(5):524-532. doi: 10.1016/j.arcmed.2022.06.005. Epub 2022 Jul 6. PMID: 35803828.

3. 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 Mar 22;164(6):659-63. doi: 10.1001/archinte.164.6.659. PMID: 15037495.

4. Bosi A, Xu Y, Gasparini A, Wettermark B, Barany P, Bellocco R, Inker LA, Chang AR, McAdams-DeMarco M, Grams ME, Shin JI, Carrero JJ. Use of nephrotoxic medications in adults with chronic kidney disease in Swedish and US routine care. Clin Kidney J. 2021 Oct 29;15(3):442-451. doi: 10.1093/ckj/sfab210. PMID: 35296039; PMCID: PMC8922703.

5. Carey RM, Moran AE, Whelton PK. Treatment of Hypertension: A Review. JAMA. 2022 Nov 8;328(18):1849-1861. doi: 10.1001/jama.2022.19590. PMID: 36346411.

6. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int. 2021 Mar;99(3S):S1-S87. doi: 10.1016/j.kint.2020.11.003. PMID: 33637192.

7. SPRINT Research Group, Lewis CE, Fine LJ, Beddhu S, Cheung AK, Cushman WC, Cutler JA, Evans GW, Johnson KC, Kitzman DW, Oparil S, Rahman M, Reboussin DM, Rocco MV, Sink KM, Snyder JK, Whelton PK, Williamson JD, Wright JT Jr, Ambrosius WT. Final Report of a Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2021 May 20;384(20):1921-1930. doi: 10.1056/NEJMoa1901281. PMID: 34010531.

8. Foti KE, Wang D, Chang AR, Selvin E, Sarnak MJ, Chang TI, Muntner P, Coresh J. Potential implications of the 2021 KDIGO blood pressure guideline for adults with chronic kidney disease in the United States. Kidney Int. 2021 Mar;99(3):686-695. doi: 10.1016/j.kint.2020.12.019. PMID: 33637204; PMCID: PMC7958922.

9. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC Scientific Document Group. Linee guida ESC 2021 per la prevenzione delle malattie cardiovascolari nella pratica clinica elaborate dalla Task Force per la prevenzione delle malattie cardiovascolari nella pratica clinica costituita da rappresentanti della Società Europea di Cardiologia e di 12 società medico-scientifiche con il contributo straordinario dell'Associazione Europea di Cardiologia Preventiva (EAPC) [2021 ESC Guidelines on cardiovascular disease prevention in clinical practice]. G Ital Cardiol (Rome). 2022 Jun;23(6 Suppl 1):e3-e115. Italian. doi: 10.1714/3808.37926. PMID: 35708476.

10. Ku E, Lee BJ, Wei J, Weir MR. Hypertension in CKD: Core Curriculum 2019. Am J Kidney Dis. 2019 Jul;74(1):120-131. doi: 10.1053/j.ajkd.2018.12.044. Epub 2019 Mar 19. PMID: 30898362.

11. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013 Jun 4;158(11):825-30. doi: 10.7326/0003-4819-158-11-201306040-00007. PMID: 23732715.

12. Drawz PE, Beddhu S, Kramer HJ, Rakotz M, Rocco MV, Whelton PK. Blood Pressure Measurement: A KDOQI Perspective. Am J Kidney Dis. 2020 Mar;75(3):426-434. doi: 10.1053/j.ajkd.2019.08.030. Epub 2019 Dec 18. PMID: 31864820; PMCID: PMC7338147.

13. Crim MT, Yoon SS, Ortiz E, Wall HK, Schober S, Gillespie C, Sorlie P, Keenan N, Labarthe D, Hong Y. National surveillance definitions for hypertension prevalence and control among adults. Circ Cardiovasc Qual Outcomes. 2012 May;5(3):343-51. doi: 10.1161/CIRCOUTCOMES.111.963439. Epub 2012 May 1. PMID: 22550130; PMCID: PMC3407684.

14. Frieden TR. Sodium Reduction--Saving Lives by Putting Choice Into Consumers' Hands. JAMA. 2016 Aug 9;316(6):579-80. doi: 10.1001/jama.2016.7992. PMID: 27249371.

15. Braam B, Taler SJ, Rahman M, Fillaus JA, Greco BA, Forman JP, Reisin E, Cohen DL, Saklayen MG, Hedayati SS. Recognition and Management of Resistant Hypertension. Clin J Am Soc Nephrol. 2017 Mar 7;12(3):524-535. doi: 10.2215/CJN.06180616. Epub 2016 Nov 28. PMID: 27895136; PMCID: PMC5338706.

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for

reporting observational studies. Int J Surg. 2014 Dec;12(12):1495-9. doi: 10.1016/j.ijsu.2014.07.013. Epub 2014 Jul 18. PMID: 25046131.

17. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013 Feb 4;17(1):204. doi: 10.1186/cc11454. PMID: 23394211; PMCID: PMC4057151.

18. Negi S., Koreeda D., Kobayashi, S, Iwashita Y, Shigematu T. Renal replacement therapy for acute kidney injury. *Ren Replace Ther*. 2016; (2), 31, 1-7. https://doi.org/10.1186/s41100-016-0043-1

19. Leaf DE, Waikar SS. IDEAL-ICU in Context. Clin J Am Soc Nephrol. 2019 Aug 7;14(8):1264-1267. doi: 10.2215/CJN.01180119. Epub 2019 Jul 17. PMID: 31315886; PMCID: PMC6682815.

20. Klahr S. The modification of diet in renal disease study. N Engl J Med. 1989 Mar 30;320(13):864-6. doi: 10.1056/NEJM198903303201310. PMID: 2494456.

21. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lewis J, Phillips RA, Toto RD, Middleton JP, Rostand SG; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA. 2002 Nov 20;288(19):2421-31. doi: 10.1001/jama.288.19.2421. Erratum in: JAMA. 2006 Jun 21;295(23):2726. PMID: 12435255.

22. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, Lesti M, Perticucci E, Chakarski IN, Leonardis D, Garini G, Sessa A, Basile C, Alpa M, Scanziani R, Sorba G, Zoccali C, Remuzzi G; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. Lancet. 2005 Mar 12-18;365(9463):939-46. doi: 10.1016/S0140-6736(05)71082-5. PMID: 15766995.

23. Magriço R, Bigotte Vieira M, Viegas Dias C, Leitão L, Neves JS. BP Reduction, Kidney Function Decline, and Cardiovascular Events in Patients without CKD. Clin J Am Soc Nephrol. 2018 Jan 6;13(1):73-80. doi: 10.2215/CJN.05510517. Epub 2017 Nov 3. PMID: 29101186; PMCID: PMC5753311.

24. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman BI, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgram D, Yee J; SPRINT Research Group. Effects of Intensive BP Control in CKD. J Am Soc Nephrol. 2017 Sep;28(9):2812-2823. doi: 10.1681/ASN.2017020148. Epub 2017 Jun 22. PMID: 28642330; PMCID: PMC5576945.

25. Ku E, Gassman J, Appel LJ, Smogorzewski M, Sarnak MJ, Glidden DV, Bakris G, Gutiérrez OM, Hebert LA, Ix JH, Lea J, Lipkowitz MS, Norris K, Ploth D, Pogue VA, Rostand SG, Siew ED, Sika M, Tisher CC, Toto R, Wright JT Jr, Wyatt C, Hsu CY. BP Control and Long-Term Risk of ESRD and Mortality. J Am Soc Nephrol. 2017 Feb;28(2):671-677. doi: 10.1681/ASN.2016030326. Epub 2016 Aug 11. PMID: 27516235; PMCID: PMC5280023.

26. Tsai WC, Wu HY, Peng YS, Yang JY, Chen HY, Chiu YL, Hsu SP, Ko MJ, Pai MF, Tu YK, Hung KY, Chien KL. Association of Intensive Blood Pressure Control and Kidney Disease Progression in Nondiabetic Patients With Chronic Kidney Disease: A Systematic Review and Meta-analysis. JAMA Intern Med. 2017 Jun 1;177(6):792-

799. doi: 10.1001/jamainternmed.2017.0197. Erratum in: JAMA Intern Med. 2017 Nov 1;177(11):1703. PMID: 28288249; PMCID: PMC5818822.

27. Chiang HP, Lee JJ, Chiu YW, Tsai JC, Hung CC, Hwang SJ, Chen HC. Systolic blood pressure and outcomes in stage 3-4 chronic kidney disease patients: evidence from a Taiwanese cohort. Am J Hypertens. 2014 Nov;27(11):1396-407. doi: 10.1093/ajh/hpu056. Epub 2014 Apr 11. PMID: 24727359; PMCID: PMC4263936.

28. Dasgupta I, Zoccali C. Is the KDIGO Systolic Blood Pressure Target <120 mm Hg for Chronic Kidney Disease Appropriate in Routine Clinical Practice? Hypertension. 2022 Jan;79(1):4-11. doi: 10.1161/HYPERTENSIONAHA.121.18434. Epub 2021 Nov 17. PMID: 34784720; PMCID: PMC8654101.

29. Kelly KJ, Burford JL, Dominguez JH. Postischemic inflammatory syndrome: a critical mechanism of progression in diabetic nephropathy. Am J Physiol Renal Physiol. 2009 Oct;297(4):F923-31. doi: 10.1152/ajprenal.00205.2009. Epub 2009 Aug 5. PMID: 19656916.

30. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH (19) Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104. doi: 10.1093/eurheartj/ehy339. Erratum in: Eur Heart J. 2019 Feb 1;40(5):475. PMID: 30165516.

31. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-3337. doi: 10.1093/eurheartj/ehab484. Erratum in: Eur Heart J. 2022 Nov 7;43(42):4468. PMID: 34458905.

32. Kula AJ, Prince DK, Flynn JT, Bansal N. BP in Young Adults with CKD and Associations with Cardiovascular Events and Decline in Kidney Function. J Am Soc Nephrol. 2021 May 3;32(5):1200-1209. doi: 10.1681/ASN.2020081156. Epub 2021 Mar 10. PMID: 33692088; PMCID: PMC8259674.

33. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright JT Jr, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman BI, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgram D, Yee J; SPRINT Research Group. Effects of Intensive BP Control in CKD. J Am Soc Nephrol. 2017 Sep;28(9):2812-2823. doi: 10.1681/ASN.2017020148. Epub 2017 Jun 22. PMID: 28642330; PMCID: PMC5576945.

34. Malhotra R, Nguyen HA, Benavente O, Mete M, Howard BV, Mant J, Odden MC, Peralta CA, Cheung AK, Nadkarni GN, Coleman RL, Holman RR, Zanchetti A, Peters R, Beckett N, Staessen JA, Ix JH. Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5: A Systematic Review and Meta-analysis. JAMA Intern Med. 2017 Oct 1;177(10):1498-1505. doi: 10.1001/jamainternmed.2017.4377. PMID: 28873137; PMCID: PMC5704908.

35. Kramer HJ, Townsend RR, Griffin K, Flynn JT, Weiner DE, Rocco MV, Choi MJ, Weir MR, Chang TI, Agarwal R, Beddhu S. KDOQI US Commentary on the 2017 ACC/AHA Hypertension Guideline. Am J Kidney Dis. 2019 Apr;73(4):437-458. doi: 10.1053/j.ajkd.2019.01.007. PMID: 30905361; PMCID: PMC6740329.

36. Ott C, Schmieder RE. Diagnosis and treatment of arterial hypertension 2021. Kidney Int. 2022 Jan;101(1):36-46. doi: 10.1016/j.kint.2021.09.026. Epub 2021 Oct 29. PMID: 34757122.

37. An J, Kurella Tamura M, Odden MC, Ni L, Thomas IC, Montez-Rath ME, Sim JJ. Prevalence of Apparent Treatment-Resistant Hypertension in Chronic Kidney Disease in Two Large US Health Care Systems. Clin J Am Soc Nephrol. 2022 Oct;17(10):1457-1466. doi: 10.2215/CJN.04110422. Epub 2022 Sep 9. PMID: 36400564; PMCID: PMC9528269.

38. Hung SC, Kuo KL, Peng CH, Wu CH, Lien YC, Wang YC, Tarng DC. Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease. Kidney Int. 2014 Mar;85(3):703-9. doi: 10.1038/ki.2013.336. Epub 2013 Sep 11. PMID: 24025647

39. Ronco C, Verger C, Crepaldi C, Pham J, De Los Ríos T, Gauly A, Wabel P, Van Biesen W; IPOD-PD Study Group. Baseline hydration status in incident peritoneal dialysis patients: the initiative of patient outcomes in dialysis (IPOD-PD study)†. Nephrol Dial Transplant. 2015 May;30(5):849-58. doi: 10.1093/ndt/gfv013. Epub 2015 Mar 11. PMID: 25762355; PMCID: PMC4425480.

40. Chen SC, Hung CC, Tsai YC, Huang JC, Kuo MC, Lee JJ, Chiu YW, Chang JM, Hwang SJ, Chen HC. Association of cholesterol levels with mortality and cardiovascular events among patients with CKD and different amounts of proteinuria. Clin J Am Soc Nephrol. 2013 Nov;8(11):1915-26. doi: 10.2215/CJN.02350213. Epub 2013 Aug 8. PMID: 23929929; PMCID: PMC3817903.

41. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006 Jul;17(7):2034-47. doi: 10.1681/ASN.2005101085. Epub 2006 May 31. PMID: 16738019.

42. Weir MR, Lakkis JI, Jaar B, Rocco MV, Choi MJ, Kramer HJ, Ku E. Use of Renin-Angiotensin System Blockade in Advanced CKD: An NKF-KDOQI Controversies Report. Am J Kidney Dis. 2018 Dec;72(6):873-884. doi: 10.1053/j.ajkd.2018.06.010. Epub 2018 Sep 7. PMID: 30201547.

43. Bhandari S, Mehta S, Khwaja A, Cleland JGF, Ives N, Brettell E, Chadburn M, Cockwell P; STOP ACEi Trial Investigators. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease. N Engl J Med. 2022 Dec 1;387(22):2021-2032. doi: 10.1056/NEJMoa2210639. Epub 2022 Nov 3. PMID: 36326117.

44. Lai M, Gao Y, Tavakol M, Freise C, Lee BK, Park M. Pretransplant Dialysis and Preemptive Transplant in Living Donor Kidney Recipients. Kidney360. 2022 Apr 18;3(6):1080-1088. doi: 10.34067/KID.0007652021. PMID: 35845334; PMCID: PMC9255866.

45. Li PK, Chow KM, Van de Luijtgaarden MW, Johnson DW, Jager KJ, Mehrotra R, Naicker S, Pecoits-Filho R, Yu XQ, Lameire N. Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol. 2017 Feb;13(2):90-103. doi: 10.1038/nrneph.2016.181. Epub 2016 Dec 28. PMID: 28029154.

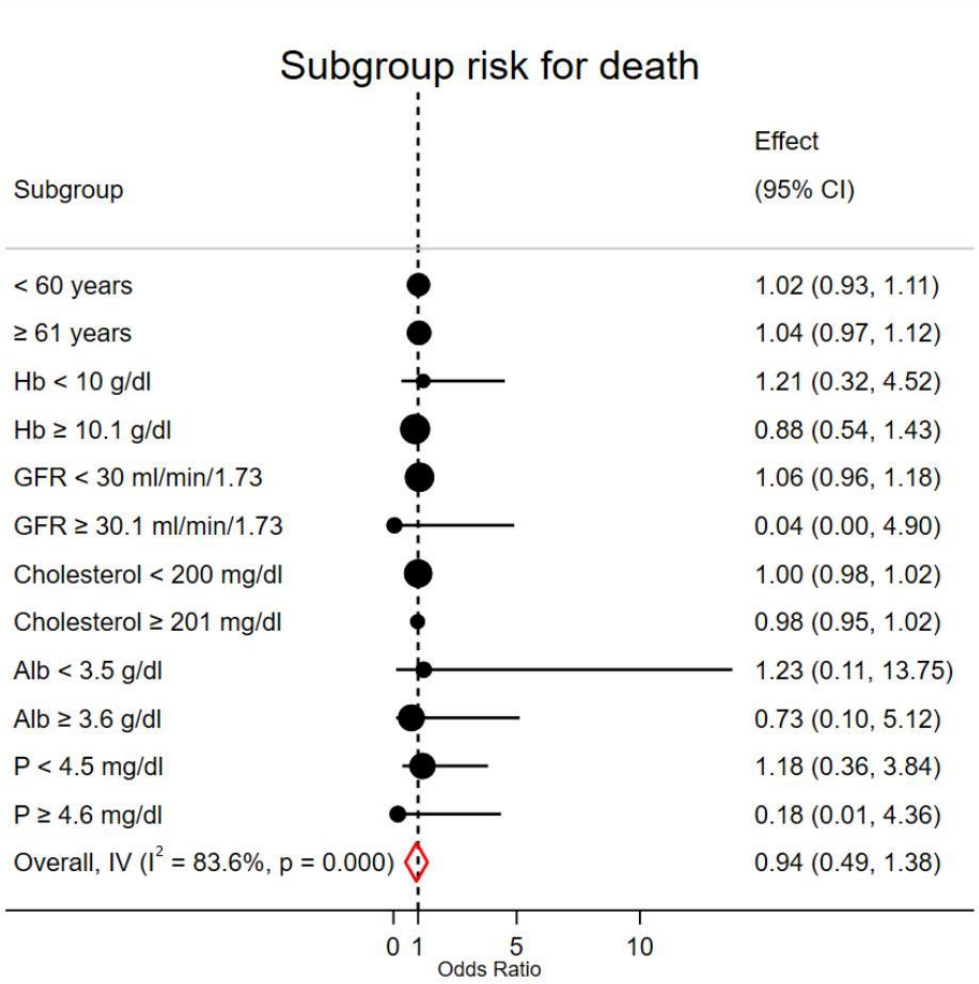
46. DeVita MV, Khine SK, Shivarov H. Novel Approaches to Arteriovenous Access Creation, Maturation, Suitability, and Durability for Dialysis. Kidney Int Rep. 2020 Mar 3;5(6):769-778. doi: 10.1016/j.ekir.2020.02.1024. PMID: 32518859; PMCID: PMC7270716.

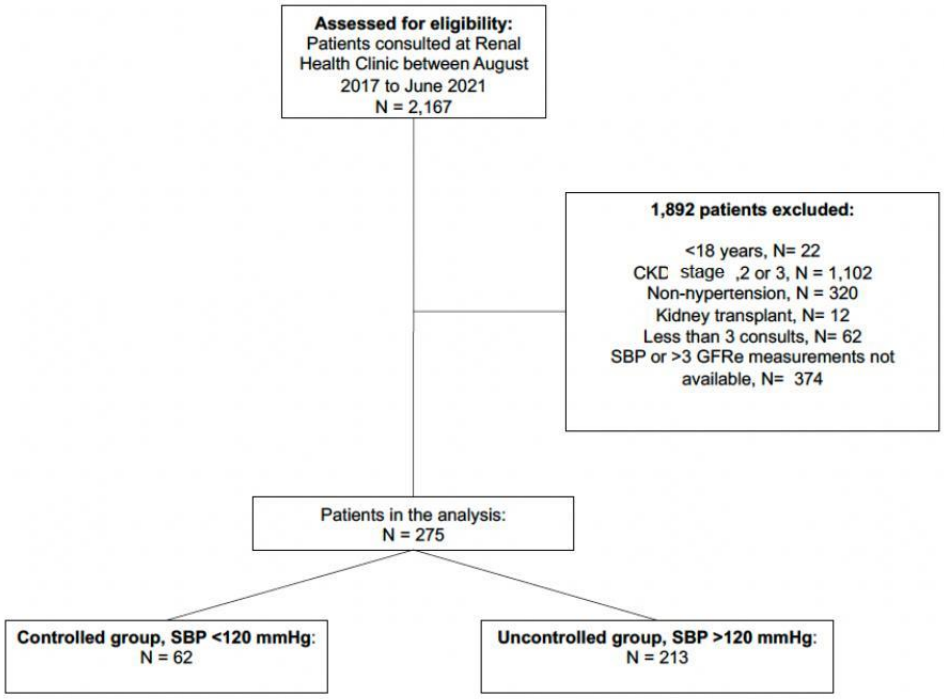
Figure legends

Figure 1. Flow chart of the study.

Figure 2. Forest Plot for KRT by subgroups

Figure 3. Forest Plot mortality risk by subgroups


Subgroup risk for death
Subgroup
Effect
(95% CI)
< 60 years
1.02 (0.93, 1.11)
≥ 61 years
1.04 (0.97, 1.12)
Hb < 10 g/dl
1.21 (0.32, 4.52)
Hb ≥ 10.1 g/dl
0.88 (0.54, 1.43)
GFR < 30 ml/min/1.73
1.06 (0.96, 1.18)
GFR ≥ 30.1 ml/min/1.73
0.04 (0.00, 4.90)
Cholesterol < 200 mg/dl
1.00 (0.98, 1.02)
Cholesterol ≥ 201 mg/dl
0.98 (0.95, 1.02)
Alb < 3.5 g/dl
1.23 (0.11, 13.75)
Alb ≥ 3.6 g/dl
0.73 (0.10, 5.12)
P < 4.5 mg/dl
1.18 (0.36, 3.84)
P ≥ 4.6 mg/dl
0.18 (0.01, 4.36)
Overall, IV (I^2 = 83.6%, p = 0.000)
0.94 (0.49, 1.38)
0 1 5 10
Odds Ratio


Assessed for eligibility:
Patients consulted at Renal Health Clinic between August 2017 to June 2021
N = 2,167
1,892 patients excluded:
<18 years, N= 22
CKD stage ,2 or 3, N = 1,102
Non-nypertension, N = 320
Kidney transplant, N= 12
Less than 3 consults, N= 62
SBP or >3 GFRe measurements not available, N= 374
Patients in the analysis:
N = 275
Controlled group, SBP <120 mmHg:
N = 62
Uncontrolled group, SBP >120 mmHg:
N = 213

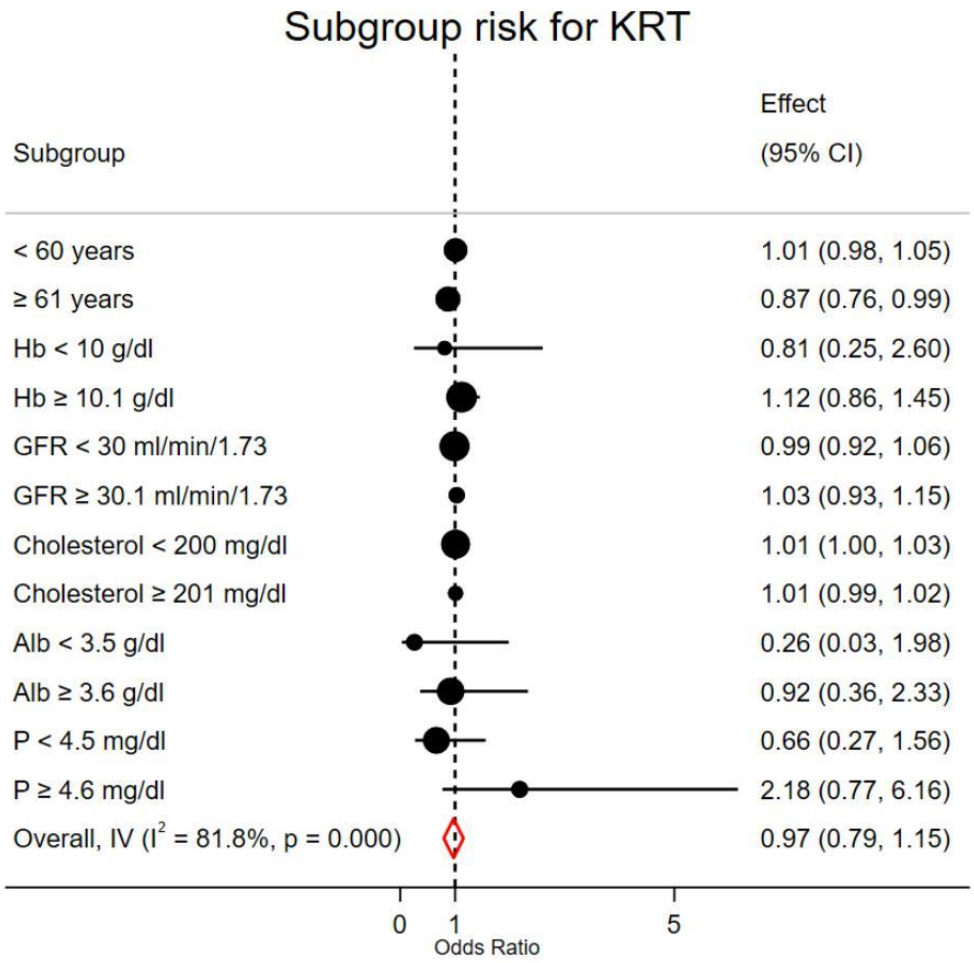

Subgroup risk for KRT
Subgroup
Effect
(95% CI)
< 60 years
1.01 (0.98, 1.05)
≥ 61 years
0.87 (0.76, 0.99)
Hb < 10 g/dl
0.81 (0.25, 2.60)
Hb ≥ 10.1 g/dl
1.12 (0.86, 1.45)
GFR < 30 ml/min/1.73
0.99 (0.92, 1.06)
GFR ≥ 30.1 ml/min/1.73
1.03 (0.93, 1.15)
Cholesterol < 200 mg/dl
1.01 (1.00, 1.03)
Cholesterol ≥ 201 mg/dl
1.01 (0.99, 1.02)
Alb < 3.5 g/dl
0.26 (0.03, 1.98)
Alb ≥ 3.6 g/dl
0.92 (0.36, 2.33)
P < 4.5 mg/dl
0.66 (0.27, 1.56)
P ≥ 4.6 mg/dl
2.18 (0.77, 6.16)
Overall, IV (I^2 = 81.8%, p = 0.000)
0.97 (0.79, 1.15)
0
1
5
Odds Ratio

Tabla 5. Subgroup analysis for mortality risk

Subgruop	Patients	Events	HR	IC	P interacción
Age					
< 60	129	5	1.02 (p= 0.62)	0.93 – 1.11	0.081
≥ 61	146	31	1.04 (p=0.20)	0.97 – 1.12	
Hb					
< 10	37	4	1.21 (p= 0.76)	0.32 – 4.52	**0.040**
≥ 10.1	234	12	0.88 (p=0.61)	0.54 – 1.43	
eGFR					
< 30	223	14	1.06 (p= 0.23)	0.96 – 1.18	0.521
≥ 30.1	51	2	0.04 (p=0.19)	0.00 – 4.90	
Cholesterol					
< 200	205	10	1.00 (p=0.78)	0.98 – 1.02	0.260
≥ 201	41	6	0.98 (p=056)	0.95 – 1.02	
Albumin					
< 3.5	53	6	1.23 (p=0.86)	0.11 – 13.75	0.075
≥ 3.6	179	10	0.73 (p= 0.75)	0.10 – 5.12	
Phosphate					
< 4.5	170	11	1.18 (p=0.77)	0.36 – 3.84	0.483
≥ 4.6	55	4	0.18 (p=0.29)	0.00 – 4.36	
Total	275	36	0.94	0.49 – 1.39	

eGFR, estimated glomerular filtration rate.

Table 1. Baseline clinical characteristics according to groups of SBP

Variable	Controlled SBP <120 mmHg (n = 62)	Uncontrolled SBP >120 mmHg (n = 213)	Total (n = 275)	P
Age, years	62 (42 – 70)	61 (49 – 79)	61 (49 – 71)	0.38
Male sex (%)	33 (53.23)	104 (48.83)	137 (49.82)	0.54
Systolic blood pressure, mmHg	111 (108 – 116)	140 (130 – 160)	131 (124 – 155)	< 0.01 *
Dyastolic blood pressure, mmHg	70 (60 – 78)	80 (73 – 88)	80 (70 – 86)	< 0.01 *
Creatinine mg/dL	2.8 (2.4 – 3.3)	2.9 (2.4 – 3.26)	2.8 (2.4 – 3.3)	0.60
GFRe, ml/min	21.24 (16.13 – 30.19)	20.3 (15.5 – 26.88)	20.41 (15.56 – 27.32)	0.21
Chronic kidney disease stage 4 (%)	38 (61.29)	134 (65.05)	172 (64.18)	0.58
Chronic kidney disease stage 5 (%)	8 (13.79)	36 (18)	44 (17.05)	0.29
Hemoglobin, gr/dL	11.7 (10.8 – 12.5)	11.5 (10.6 – 12.7)	11.6 (10.6 – 12.6)	0.65
Glucose, mg/dL	95 (87 – 114)	104 (90 – 126)	101 (88 – 120)	0.07 ţ
Urea, mg/dL	100 (78.5 – 141)	105.6 (8 – 135)	104 (84 – 136)	0.42
Uric acid, mg/dL	6.7 (5.3 – 8)	6.4 (5.3 – 8)	6.6 (5.3 – 8)	0.79
Cholesterol, mg/dL	144.5 (129 – 173)	155 (131 – 191)	154 (131 – 187)	0.02 *
Serum albumin	4 (3.7 – 4.4)	4 (3.6 – 4.3)	4 (3.6 – 4.3)	0.49
Serum sodium	139 (138 – 141.5)	139 (138 – 141)	139 (138 – 141)	0.63
Serum potassium	4.6 (3.9 – 5.2)	4.8 (3.9 – 5.3)	139 (3.9 – 5.2)	0.38
Serum calcium	9.1 (8.7 – 9.4)	9.2 (8.8 – 9.5)	9.2 (8.8 – 9.5)	0.68
Serum phosphate	3.81 (3.45 – 4.55)	4.1 (3.6 – 4.6)	4.1 (3.6 – 4.6)	0.11 ţ
Proteinuria, gr /day	0 (0 – 0)	0 (0 – 0.71)	0 (0 – 0.52)	0.01 *
ACEi(%)	28 (45.16)	61 (28.64)	89 (32.36)	0.01 *
ARB (%)	30 (48.39)	131 (61.50)	161 (58.55)	0.06 ţ
ß-blockers (%)	7 (11.29)	56 (26.29)	63 (22.91)	0.01 *
Calcium channel blockers (%)	15 (24.19)	89 (41.78)	104 (37.82)	0.01 *

Furosemide (%)	34 (54.84)	129 (60.56)	163 (59.27)	0.41
Statins (%)	54 (87.1)	192 (90.14)	246 (89.45)	0.49
Calcium Carbonate (%)	4 (6.45)	12 (5.63)	16 (5.82)	0.80
Calcitriol (%)	6 (9.68)	19 (8.92)	25 (9.09)	0.85
Alopurinol (%)	51 (83.61)	174 (81.69)	225 (82.12)	0.73
Vitamin D3 (%)	7 (11.29)	35 (16.43)	42 (15.27)	0.32
Sodium Bicarbonate (%)	9 (14.52)	30 (14.08)	39 (14.18)	0.93
Hypoglycemic treatment (%)	3 (4.84)	16 (7.51)	19 (6.91)	0.46
Insulin treatment (%)	22 (35.48)	97 (45.75)	119 (43.43)	0.15 ţ
Vitamin B complex (%)	1 (1.61)	6 (2.87)	7 (2.58)	0.58
Folic acid (%)	3 (4.84)	4 (1.89)	7 (2.55)	0.21
Aspirin (%)	4 (6.45)	19 (8.96)	23 (8.39)	0.53
Iron (%)	10 (16.13)	23 (10.85)	33 (12.04)	0.26
Gabapentin (%)	4 (6.45)	21 (9.95)	25 (9.16)	0.40
Levotiroxin (%)	4 (6.45)	14 (6.64)	18 (6.59)	0.95
Tamsulosin (%)	0	9 (4.25)	9 (3.28)	0.09 ţ
Omeprazol (%)	4 (6.45)	3 (1.42)	7 (2.55)	0.04 *
Outcomes				
Kidney replacement therapy	8 (12.9)	28 (13.15)	36 (13.09)	0.96
Hemodialysis (%)	5 (8.06)	10 (4.69)	15 (5.45)	0.44
Peritoneal dialysis (%)	3 (4.84)	18 (8.45)	21 (7.64)	
Dead on follow up	1 (1.61)	15 (7.04)	16 (5.82)	0.13
Days of follow up	641 (434 – 1127)	454 (255 – 681)	490 (272 – 787)	< 0.01

Continuous data presented as median and inter-quartile range, compared with the Wilcoxon Rank test (Mann Whitney U). Categorical data presented in number and percentage and compared with chi-square or Fisher's exact test as appropriate. * Statistical significance; $p<0.05$ ţ Included in the bivariate analysis; $p<0.20$

ACEi, angiotensin converting enzyme inhibitors; ARB, antagonist receptor blockers; eGFR, estimated glomerular filtration rate.

Table 2. Incidence rate of kidney replacement therapy and death according to systolic blood pressure groups.

Group	Patient - year	Events	Rate (1000 patient - year)	LIC	UIC
Kidney replacement therapy					
Controlled	92.27	8	86.69	43.35	173.35
uncontrolled	295.87	26	87.87	59.83	129.06
Total	388.15	34	87.59	62.58	122.59
Mortality					
Controlled	109.44	1	9.13	1.28	64.86
uncontrolled	296.27	14	47.25	27.98	79.78
Total	405	15	36.97	22.28	61.32

Table 3. Bivariate and multivariate Cox regression analysis of factors related to kidney replacement therapy of CKD patients.

Predictors	Bivariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Uncontrolled group	0.55 (0.70-3.44)	0.275	0.85 (0.31-2.32)	0.756
Cholesterol	1.00 (1.00-1.01)	0.008	**1.01 (1.00-1.02)**	**0.002**
Age	0.97 (0.96-0.99)	0.014	**0.97 (0.94-0.99)**	**0.040**
Phosphate	1.47 (0.99-2.17)	0.055	1.07 (.063-1.81)	0.787
eGFR	0.95 (0.91-1.00)	0.058	**0.93 (0.86-0.99)**	**0.049**
ß-blockers	1.80 (0.88-3.69)	0.104	2.44 (0.90-6.60)	0.077
Omeprazole	3.07 (0.73-12.93)	0.125	1.49(0.94-23.58)	0.776
Proteinuria	1.00 (0.99-1.00)	0.234		
ACEi	0.63 (0.29-1.35)	0.238		
Insulin	1.41 (0.72-2.78)	0.313		
Tamsulosin	1.75 (0.41-7.36)	0.440		
Calcium blockers	1.30 (0.65-2.58)	0.444		
Glucose	0.99 (0.98-1.00)	0.498		
ARB	1.03 (0.52-2.023)	0.920		

ACEi, angiotensin converting enzyme inhibitors; ARB, antagonist receptor blockers; eGFR, estimated glomerular filtration rate.

Table 4 Bivariate and multivariate Cox regression analysis of factors related to mortality risk among CKD stages 4-5 patients.

Predictors	Bivariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Cholesterol	1.01 (0.99-1.02)	0.050	**1.01 (1.00-1.02)**	**0.029**
Uncontrolled group	**6.26 (0.81-47.92)**	**0.077**	**6.47 (0.78-53.27)**	**0.082**
Omeprazole	5.53 (0.71-42.74)	0.101	10.04 (0.91-110.25)	0.059
ECAi	2.42 (0.83-6.98)	0.102	**3.63 (1.12-11.73)**	**0.031**
Age	1.03 (0.99-1.07)	0.126	1.01 (0.97-1.05)	0.597
ß-blockers	2.21 (0.77-6.32)	0.135	2.25 (0.68-7.45)	0.182
Proteinuria	0.48 (0.11-2.02)	0.324		
ARB	0.59 (0.20-1.70)	0.333		
Insulin	1.56 (0.56-4.33)	0.391		
Tamsulosin	2.27 (0.29-3.65)	0.428		
eGFR	0.97 (0.92-1.03)	0.494		
Glucose	0.99 (0.98-1.00)	0.613		
Calcium blockers	1.22 (0.43-3.45)	0.702		
Phosphate	1.12 (0.55-2.27)	0.737		

ACEi, angiotensin converting enzyme inhibitors; ARB, antagonist receptor blockers; eGFR, estimated glomerular filtration rate.