Nephrol Dial Transplant (2021) 36: 512–519
doi: 10.1093/ndt/gfaa107
Advance Access publication 24 June 2020

ndt
Nephrology Dialysis Transplantation

ORIGINAL ARTICLE

Measured sodium excretion is associated with CKD progression: results from the KNOW-CKD study

Minjung Kang[1], Eunjeong Kang[2], Hyunjin Ryu[1], Yeji Hong[3], Seung Seok Han[1], Sue K. Park[4], Young Youl Hyun[5], Su Ah Sung[6], Soo Wan Kim[7], Tae-Hyun Yoo[8], Jayoun Kim[9], Curie Ahn[1] and Kook-Hwan Oh[1]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [2]Department of Internal Medicine, Ewha Womans University College of Medicine, Ewha Womans University Seoul Hospital, Seoul, Republic of Korea, [3]Rehabilitation Medical Research Center, Korea workers' Compensation and Welfare Service Incheon Hospital, Republic of Korea, [4]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, [5]Department of Internal Medicine, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Republic of Korea, [6]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University, Seoul, Republic of Korea, [7]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea, [8]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea and [9]Medical Research Collaborating Center, Seoul National University Hospital and Seoul National University College of Medicine, Seoul, Korea

Correspondence to: Kook-Hwan Oh; E-mail: ohchris@hanmail.net

ABSTRACT

Background. Diet is a modifiable factor of chronic kidney disease (CKD) progression. However, the effect of dietary salt intake on CKD progression remains unclear. Therefore, we analyzed the effect of dietary salt intake on renal outcome in Korean patients with CKD.

Methods. We measured 24-h urinary sodium (Na) excretion as a marker of dietary salt intake in the prospective, multi-center, longitudinal KoreaN cohort study for Outcome in patients With CKD (KNOW-CKD). Data were analyzed from CKD patients at Stages G3a to G5 ($n = 1254$). We investigated the association between dietary salt intake and CKD progression. Patients were divided into four quartiles of dietary salt intake, which was assessed using measured 24-h urinary Na excretion. The study endpoint was composite renal outcome, which was defined as either halving the estimated glomerular filtration rate or developing end-stage renal disease.

Results. During a median (interquartile range) follow-up of 4.3 (2.8–5.8) years, 480 (38.7%) patients developed the composite renal event. Compared with the reference group (Q2, urinary Na excretion: 104.2 $\leq$ Na excretion $<$ 145.1 mEq/day), the highest quartile of measured 24-h urinary Na excretion was associated with risk of composite renal outcome [Q4, urinary Na excretion $\geq$192.9 mEq/day, hazard ratio 1.8 (95% confidence interval 1.12–2.88); $P = 0.015$] in a multivariable hazards model. Subgroup analyses showed that high-salt intake was particularly associated with a higher risk of composite renal outcome in women, in patients $<$60 years of age, in those with uncontrolled hypertension and in those with obesity.

Conclusions. High salt intake was associated with increased risk of progression in CKD.

Keywords: chronic kidney disease, dietary salt intake, renal progression

INTRODUCTION

Lifestyle in general, and particularly diet, is a modifiable risk factor for chronic kidney disease (CKD) progression [1]. CKD itself is a risk factor for cardiovascular diseases and death [2]. Therefore, it is important to prevent CKD progression in its early stages [3, 4]. We focused on educating patients on their dietary habits, which are modifiable factors in the treatment of CKD.

The average salt intake in patients with CKD from the USA, the Netherlands, the UK, Turkey, Italy, Australia, Denmark and Korea was 9.5 g/day [5]. The average salt intake in general populations of the USA, the UK, Japan, China, Italy, Belgium, Finland, Germany, New Zealand and the Netherlands was 9.9 g/day [6]. Because of the detrimental effects of high-salt intake on blood pressure and cardiovascular disease [7, 8], many countries have attempted to reduce average salt intake [9]. According to the Korea National Health and Nutrition Examination Survey [10], the average daily salt intake in Koreans decreased from 11.0 to 8.3 g over the last 8 years. A person's diet is affected by region, socioeconomic status and culture [11–13]. Therefore, studies regarding diet and dietary guidelines must reflect the characteristics of respective races and cultures.

The current guidelines recommend <5 g of salt intake per day [14]. This guideline is based on studies showing that salt restriction reduced blood pressure and proteinuria [15, 16]. However, these studies did not analyze renal outcomes associated with a high salt diet, such as incident end-stage renal disease (ESRD) or estimated glomerular filtration rate (eGFR) halving. Therefore, there is insufficient evidence that high-salt diet is associated with CKD progression.

A few studies, including the Chronic Renal Insufficiency Cohort (CRIC) study, have demonstrated a significant association between high salt intake and CKD progression in patients with CKD [17–19]. In contrast, other studies have shown no association between urinary sodium (Na) excretion and kidney failure in CKD patients [20, 21]. However, most of these previous studies are not generalizable to the entire CKD population because they were performed in specific subgroups of CKD subjects, such as nondiabetic CKD, diabetic CKD or advanced CKD patients (eGFR <30 mL/min/1.73 m^2). The CRIC study covers the entire CKD population, however, the race is mostly Caucasian and African Americans. Therefore, it is difficult to apply the results directly to the Asian CKD population.

Meanwhile, in the general population, a U-shaped relationship was shown between salt diet and incident CKD only in the group with hypertension (HTN) [22]. Therefore, the effect of urinary Na excretion on CKD progression remains controversial not only in the general population, but also in CKD patients.

This study analyzed patients with variable etiologies of CKD. We sought to demonstrate the effect of dietary salt intake, as assessed by measured 24-h urinary Na excretion, on renal outcomes in CKD patients using a dataset from a prospective CKD cohort, entitled the KoreaN cohort study for Outcome in patients With CKD (KNOW-CKD).

MATERIALS AND METHODS

Study participants

KNOW-CKD cohort is an ongoing nationwide, multicenter, prospective cohort study from nine tertiary hospitals in Korea [23, 24]. Between 2011 and 2016, a total of 2238 patients with CKD Stages 1–5 (predialysis) and aged between 20 and 75 years old was enrolled. Patients with previous history of dialysis, any organ transplant, heart failure (the New York Heart Association (NYHA) functional classification III or IV), known cirrhosis, history of cancer and pregnant women were excluded. At enrollment, the subjects collected 24-h urine samples for Na excretion. Because patients with relatively preserved kidney function tended to follow a high salt diet [17], we excluded subjects with eGFR ≥60 mL/min/1.73 m^2 ($n = 785$). Patients were also excluded if they did not collect 24-h urine specimens successfully ($n = 4$), did not have baseline 24-h urinary Na excretion ($n = 186$) or had extreme urinary sodium excretion (>1000 mEq/day or <20 mEq/day) ($n = 9$). Ultimately, 1254 patients were included (Supplementary data, Figure S1). These patients were divided according to quartile of measured 24-h urinary Na excretion. The study design was approved by the interstitial review boards of the participating centers and complies with the Declaration of Helsinki.

Data collection and measurements

Information regarding patient demographic characteristics, medical history and medications was collected by self-report and review of the medical records. The baseline laboratory data included hemoglobin, serum albumin, creatinine, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride. The measured 24-h urinary Na excretion was used to assess daily salt intake [25]. Urine samples that were collected inadequately (urine <500 mL/day) were excluded. For sensitivity analysis, spot urinary samples were used for Na and creatinine concentrations. Patients were excluded from sensitivity analysis if they did not have baseline spot urinary samples ($n = 38$). The Tanaka equation was used to estimate 24-h urinary Na excretion from spot urine Na [26]. The formula is: $21.98 \times ([\text{spot Na (mmol/L)/spot Cr (mg/dL)} \times 10] \times \{[-2.04 \times \text{age (years)}] + [14.89 \times \text{weight (kg)}] + [16.14 \times \text{height (cm)}] - 2244.45\})^{0.392}$. Serum creatinine was measured using an isotope dilution mass spectrometry-calibrated method at a central laboratory. The eGFR was calculated by the CKD Epidemiology Collaboration equation [27]. Random urine sodium and creatinine were measured at a central laboratory. Uncontrolled HTN was defined as systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg [28]. Body weight (BW)-adjusted dietary protein intake (DPI) was defined as estimated DPI/BW (g/day/kg BW), wherein estimated DPI was $6.25 \times [\text{24-h urinary urea (mg/day)}/1000 + 0.03 \times \text{BW (kg)}] + [\text{24-h urinary protein (mg/day)}/1000]$ [29]. The recommended dietary allowance was a BW-adjusted DPI ≥0.8 g/day/kg BW [30].

Outcomes

The primary outcome was the composite renal outcome, which was defined as eGFR halving or occurrence of ESRD. ESRD was defined as initiation of dialysis or kidney transplantation. The subjects who were lost to follow-up were censored at the time of last visit. Survival time was calculated from enrollment to occurrence of the event or the last follow-up.

Statistical analysis

All statistical analyses were performed with SPSS software version 25 (IBM Corp., Armonk, NY, USA) and R software version 3.5.3 (www.r-projectorg; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation or as medians with interquartile ranges (IQRs). The Kolmogorov–Smirnov test was employed for the normality test. Categorical variables were expressed as numbers and percentages. To compare the clinical characteristics according to quartile of urinary sodium excretion, one-way analysis of variance was used for continuous variables (Kruskal–Wallis test if not applicable), while the Chi-squared test was used for categorical variables (Fisher's exact test if not applicable). To calculate the P for trend, the

Jonckheere–Terpstra test was employed for continuous variables, and the Linear-by-Linear Association was employed for categorical variables. The hazard ratio (HR) of the composite renal outcome was analyzed using Cox proportional hazards models. Multiple covariables were adjusted. In Model 1, we adjusted for demographic information such as age, sex, body mass index (BMI) and baseline urinary creatinine. In Model 2, we further adjusted for risk factors of CKD such as urinary potassium excretion and baseline eGFR. Model 3 adjusted for CKD etiology, the presence of diabetes mellitus (DM), medications [such as diuretics and renin–angiotensin system (RAS) blockers], urinary protein excretion and SBP, in addition to factors included in Model 2. A cubic spline curve was used to explore the association between urinary Na excretion and CKD progression. The same multivariable models were applied to the cubic spline curves. Subgroup analyses were performed with respect to age group, sex, baseline eGFR, uncontrolled HTN, DM, obesity (BMI $\geq$25 kg/m^2), use of RAS blockers, use of diuretics, 24-h urinary potassium excretion and proteinuria. Spearman correlation analysis was used to estimate the correlation between urinary Na excretion and blood pressure. $P < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics are shown in Table 1 according to quartiles of measured 24-h urinary Na excretion. The median (IQR) patient age was 58.0 years (50.0–66.0), and the majority (62.0%) was male. Most patients (98.6%) also had a diagnosis of HTN. Subjects with higher urinary Na excretion tended to be male (P for trend <0.001) (Table 1). Subjects with a lower eGFR category tended to have lower urinary Na excretion (P for trend <0.001) (Table 1, Supplementary data, Figure S2). SBP and BMI increased with Na excretion. There were also more diabetic patients with higher urinary Na excretion than there were nondiabetic patients (P for trend = 0.012). Higher urinary Na excretion is associated with higher weight-adjusted DPI $\geq$0.8 g/day/kg and potassium intake (P for trend <0.001), meaning that they are eating more. Urinary excretions of creatinine, protein and chloride increased as urinary Na excretion increased. A positive correlation showed that between measured 24-h urinary sodium excretion and mean blood pressure (R^2 Linear = 0.012, P = 0.002) (Supplementary data, Figure S3).

Renal outcomes

During a median (IQR) follow-up of 4.3 years (2.8–5.8 years), 480 (38.7%) patients developed the composite renal outcome. The incidence rates of the composite renal outcome from the lowest to the highest quartile of measured 24-h urinary Na excretion were 140.2, 97.6, 116.6 and 117.8 per 1000 person-years, respectively. The adjusted HRs (95% confidence intervals) of the composite renal outcome (compared with that of the second quartile) were 1.28 (0.84–1.98), 1.69 (1.08–2.65) and 1.80 (1.12–2.88) for the first, third and fourth quartiles of urinary Na excretion, respectively (Model 3 in Table 2). The spline curve clearly demonstrated a relatively linear relationship between measured 24-h urinary Na excretion and risk of composite renal outcomes at the reference of urinary Na excretion $\geq$120.0 mEq/day (Figure 1). At measured 24-h urinary Na excretion $\geq$120.0 mEq/day, for every 100 mEq increase in daily urinary Na excretion, the risk of composite renal outcomes increased by 1.55 times in multivariable Cox regression analysis (Supplementary data, Table S1). Meanwhile, low urinary Na excretion (the lowest quartile) was not significantly associated with risk of the composite renal outcome (Table 2).

Subgroup analyses

The risk of the highest quartile of measured 24-h urinary Na excretion was compared with the risk of the second quartile of urinary Na excretion by subgroup stratified according to age (<60 or $\geq$60 years old), sex (male or female), eGFR (<45 or $\geq$45 mL/min/1.73 m^2), uncontrolled HTN (with or without), DM (with or without), obesity (BMI $\geq$25 or <25 kg/m^2), use of RAS blockers (yes or no), use of diuretics (yes or no), urinary potassium excretion (<37 or $\geq$37 mEq/day) and proteinuria (<3.5 or $\geq$3.5 g/day). The highest measured 24-h urinary Na excretion was strongly correlated with higher risks of the composite renal outcome. This was particularly true in subgroups <60 years, women and those with a lower eGFR (<45 mL/min/1.73 m^2), uncontrolled HTN, obesity, use of RAS blockers or use of diuretics (Figure 2).

Sensitivity analyses

We used the Tanaka equation to perform sensitivity analysis of estimated 24-h urinary Na excretion (calculated from spot urinary Na) in 1200 patients [26]. Estimated 24-h urinary Na excretion was divided into four groups for which the cut-off values were defined using primary analysis. When Cox regression analysis was employed, the risk of the fourth group was 1.96 times higher than the second group, which was the reference group (Model 3 in Supplementary data, Table S2). There was no significant association between the lowest urinary Na excretion and risk of renal outcome.

DISCUSSION

Although salt intake is a modifiable factor of CKD, the effect of salt intake on renal outcome is unclear. Our long-term analysis of CKD patients found that the risk of composite renal outcome was 1.8-fold higher in patients with the highest degree of dietary salt intake (fourth quartile with measured 24-h urinary Na excretion $\geq$192.9 mEq/day) than in the reference group (104.2 mEq/day $\leq$ urinary Na excretion < 145.1 mEq/day). However, there was no difference in composite renal outcome between the first and second quartiles. The risk of composite renal outcomes from high salt intake was particularly evident in subgroups of patients <60 years old, female, with lower eGFR (<45 mL/min/1.73 m^2) or uncontrolled HTN, or obesity, or RAS blockers or diuretics.

A previous study from the CRIC showed a positive association between high salt intake and risk of composite renal outcome (as defined by incident ESRD or eGFR halving) [17].

Table 1. Baseline participant characteristics

Variable	Measured 24-h urinary Na excretion (mEq/day)					P for trend
	Total ($n = 1254$)	<104.2 ($n = 314$)	104.2 to <145.1 ($n = 313$)	145.1 to <192.9 ($n = 313$)	≥192.9 ($n = 314$)	
Age, years	58.0 (50.0–66.0)	58.0 (50.0–66.0)	58.0 (50.0–66.0)	59.0 (51.0–66.0)	58.0 (48.0–65.0)	0.293
Male, *n* (%)	778 (62.0)	168 (53.5)	179 (57.2)	195 (62.3)	236 (75.2)	<0.001
Etiology of CKD, *n* (%)						0.345
Glomerulonephritis	360 (28.7)	93 (29.6)	92 (29.4)	94 (30.0)	81 (25.8)	–
Diabetic nephropathy	402 (32.1)	98 (31.2)	100 (31.9)	95 (30.4)	109 (34.7)	–
Hypertensive nephropathy	290 (23.1)	75 (23.9)	65 (20.8)	77 (24.6)	73 (23.2)	–
Polycystic kidney disease	129 (10.3)	32 (10.2)	43 (13.7)	26 (8.3)	28 (8.9)	–
Others	73 (5.8)	16 (5.1)	13 (4.2)	21 (6.7)	23 (7.3)	–
eGFR category, mL/min/1.73 m^2, *n* (%)						<0.001
45–59	322 (25.7)	61 (19.4)	93 (29.7)	77 (24.6)	91 (29.0)	–
30–44	410 (32.7)	91 (29.0)	94 (30.0)	112 (35.8)	113 (36.0)	–
15–29	406 (32.4)	117 (37.3)	102 (32.6)	102 (32.6)	85 (27.1)	–
<15	116 (9.3)	45 (14.3)	24 (7.7)	22 (7.0)	25 (8.0)	–
SBP, mmHg	128.0 (118.0–138.0)	124.5 (114.0–136.0)	128.0 (120.0–138.0)	128.0 (119.0–136.0)	130.0 (118.0–139.0)	0.037
DBP, mmHg	76.0 (69.0–83.0)	74.0 (67.0–81.0)	77.0 (69.0–85.0)	76.0 (70.0–83.0)	77.0 (69.0–85.0)	0.012
Uncontrolled HTN_2 *n* (%)	354 (28.3)	75 (23.9)	89 (28.4)	85 (27.2)	105 (33.5)	0.015
BMI, kg/m^2	24.5 (22.5–26.5)	23.6 (21.3–25.6)	24.3 (22.1–26.1)	24.7 (23.0–26.8)	25.3 (23.6–27.7)	<0.001
Use of medication						
RAS blocker, *n* (%)	1082 (86.3)	257 (81.8)	280 (89.5)	266 (85.0)	279 (88.9)	0.056
Diuretics, *n* (%)	497 (39.6)	120 (38.2)	118 (37.7)	124 (39.6)	135 (43.0)	0.188
Diabetes, *n* (%)	540 (43.1)	125 (39.8)	125 (39.9)	136 (43.5)	154 (49.0)	0.012
HTN, *n* (%)	1235 (98.6)	309 (98.4)	306 (97.8)	311 (99.4)	309 (98.7)	0.398
Cardiovascular disease, *n* (%)	251 (20.0)	61 (19.4)	69 (22.0)	66 (21.1)	55 (17.5)	0.508
DPI ≥ 0.8 g/day/kg, *n* (%)	810 (67.7)	124 (41.2)	183 (62.9)	231 (76.2)	272 (90.1)	<0.001
Laboratory findings						
eGFR, mL/min/1.73 m^2	33.7 (23.1–45.2)	29.3 (19.5 40.9)	34.7 (23.8–47.2)	33.7 (24.6–44.8)	36.3 (24.7–47.0)	<0.001
Hemoglobin, g/dL	12.0 (10.8–13.6)	11.6 (10.6–12.8)	12.0 (10.7–13.9)	12.2 (11.0–13.6)	12.6 (11.0–14.1)	<0.001
Albumin, g/dL	4.2 (3.9–4.4)	4.2 (3.9–4.4)	4.2 (3.9–4.4)	4.1 (3.9–4.4)	4.2 (3.9–4.5)	0.198
LDL-C, mg/dL	89.0 (71.0–111.0)	84.0 (69.0–103.5)	93.0 (72.0–113.5)	89.0 (71.0–115.0)	91.0 (74.0–114.0)	0.001
HDL-C, mg/dL	44.0 (36.0–54.2)	45.0 (36.0–56.0)	44.0 (36.2–54.2)	44.0 (36.0–54.0)	44.0 (37.0–54.0)	0.883
Triglyceride, mg/dL	138.0 (96.0–204.0)	127.5 (91.0–185.0)	134.0 (96.0–206.5)	144.5 (98.0–205.0)	144.0 (107.0–217.0)	0.001
Urine volume, mL	1810.0 (1500.0–2300.0)	1350.0 (1000.0–1680.0)	1700.0 (1450.0–2000.0)	1900.0 (1600.0–2200.0)	2400.0 (2070.0–2850.0)	<0.001
Urinary creatinine, mg/day	1100.0 (848.0–1396.5)	856.0 (660.0–1110.0)	1000.0 (803.0–1276.0)	1127.5 (937.0–1400.0)	1388.8 (1122.0–1610.4)	<0.001
Urinary protein, mg/day	745.5 (271.1–2076.5)	555.0 (231.0–1518.5)	652.7 (192.8–1592.8)	798.7 (338.0–2190.0)	1241.0 (374.0–3536.0)	<0.001
Urinary sodium, mEq/day	145.1 (104.0–193.0)	80.0 (62.0–95.0)	124.6 (115.0–134.0)	164.9 (156.0–178.0)	226.9 (209.6–265.0)	<0.001
Urinary potassium, mEq/day	48.0 (34.0–63.0)	33.0 (24.2–42.0)	44.5 (35.2–57.8)	51.8 (41.0–63.0)	64.7 (50.0–77.0)	<0.001
Urinary chloride, mEq/day	141.0 (99.0–189.3)	78.1 (60.0–94.0)	126.2 (112.0–138.0)	169.0 (153.0–183.5)	226.0 (204.0–263.3)	<0.001

Data are presented as median (IQR) unless otherwise indicated.

The range of the highest quartile was urinary Na excretion >194.6 mEq/day, which is similar to that in this study. However, as dietary patterns vary by race and culture, it is difficult to apply such findings, mostly based on Caucasian and African Americans, directly to Asians. Besides, in the CRIC study, when proteinuria was added as an adjustment variable, the significance of the association between urinary sodium excretion and CKD progression disappeared. In contrast, in this study, the significant association between measured 24-h urinary sodium excretion and CKD progression was maintained, even after adjustment for proteinuria. This suggests that urinary sodium excretion is an independent factor for CKD progression in this study, aside from proteinuria. Such a discrepancy between our study and CRIC study might be partly attributable to the higher incidence of composite renal event in our study (117.7/1000 person-years), as compared with that of the CRIC study (59.4/1000 person-years), resulting in higher statistical power. Other studies have shown

Table 2. Multivariable model for risk of composite renal outcome

Measured urinary sodium excretion (mEq/day)	Number of participants	Number of events (%)	Model 1		Model 2		Model 3	
			HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<104.2	308	136 (44)	1.22 (0.94 – 1.59)	0.140	0.93 (0.61 – 1.40)	0.713	1.28 (0.84 – 1.98)	0.255
104.2≤ <145.1	312	100 (32)	1 (Reference)		1 (Reference)		1 (Reference)	
145.1≤ <192.9	310	122 (39)	1.36 (1.04 – 1.77)	0.027	1.36 (0.88 – 2.11)	0.169	1.69 (1.08 – 2.65)	0.022
≥192.9	310	122 (39)	1.52 (1.14 – 2.01)	0.004	1.64 (1.04 – 2.58)	0.033	1.80 (1.12 – 2.88)	0.015
Total	1240	480 (39)	–	–	–	–	–	–

Model 1: adjusted for age, sex, BMI and urinary creatinine excretion.
Model 2: Model 1 plus urinary potassium excretion and baseline eGFR.
Model 3: Model 2 plus etiology of CKD, the presence of DM, use of diuretics, use of RAS blockers, urinary protein excretion and SBP.

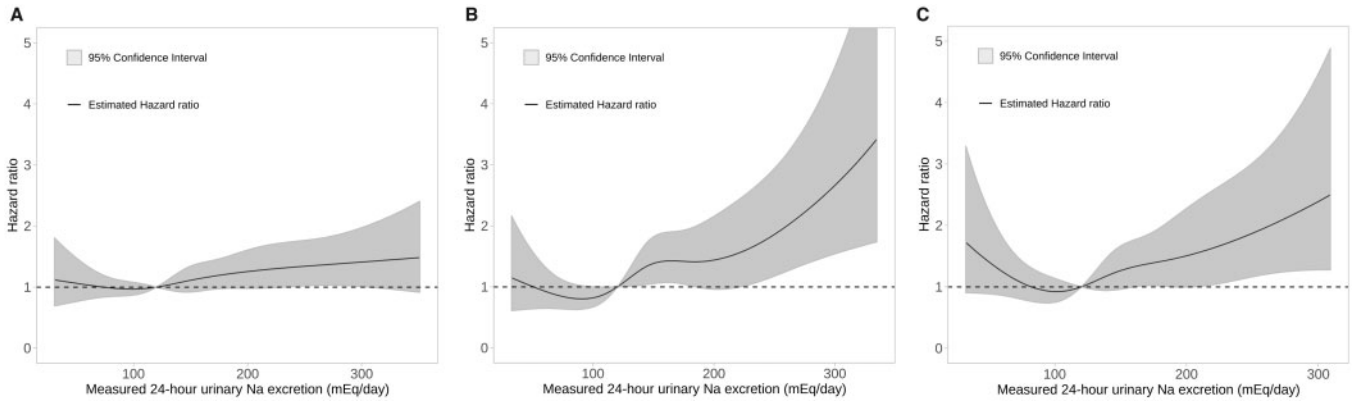

FIGURE 1: Association of measured 24-h urinary sodium excretion with HR of CKD progression in Model 1 (**a**), in Model 2 (**b**) and in Model 3 (**c**).

positive association between high-salt diet and CKD progression [18, 19, 31]. However, these studies were limited to a subgroup of CKD patients—proteinuric CKD without DM, CKD with Type 2 DM or to hypertensive CKD without DM. Meanwhile, other studies showed no association between urinary Na excretion and CKD progression in non-diabetic CKD patients [20] or in advanced CKD patients [21]. Overall, therefore, it has been controversial whether there is an association between salt intake and CKD progression. Besides, these prior findings were not generalizable to the overall CKD population.

In our study, risk of composite renal outcome in the highest quartile group (measured 24-h urinary Na excretion ≥192.9 mEq/day) was 1.8 times higher than that in the reference group. The first mechanistic explanation for this result is the positive association between urinary Na excretion and blood pressure, which is a risk factor of CKD progression [32, 33]. In particular, blood pressure was found to rise sharply in the high salt intake category (urinary Na excretion ≥217.4 mEq/day) of the general population [34]. In our analysis, the proportion of uncontrolled HTN was especially high in the highest quartile, and there was positive correlation between measured 24-h urinary Na excretion and mean blood pressure. Both CKD patients and those with HTN were salt-sensitive [35, 36]. In addition, most of our patients had HTN. Blood pressure increased sharply as daily salt intake increased, which might contribute to renal progression. Second, high salt intake attenuated the anti-proteinuric effect of RAS blockers, which may contribute to poor renal outcome [18]. In our data, subgroup analyses showed that high salt intake was particularly associated with composite renal outcome in patients using RAS blockers. This result also supported the above explanation that the anti-proteinuric effect of RAS blockers in patients with high salt intake was attenuated. However, our analysis exhibited an independent association between high salt intake and renal progression, even after adjustment for blood pressure and proteinuria. Therefore, there might be another mechanism whereby high salt intake leads to kidney damage. One animal study showed that higher salt intake was associated with higher RAS activation and progression of renal fibrosis [37]. High salt intake increased inflammation [38] and oxidative stress [39]. Through the correlation between salt intake and pulse wave velocity, salt loading affected vascular wall function regardless of blood pressure [40]. Collectively, renal fibrosis, inflammation, oxidative stress and arterial stiffness may all contribute to deterioration of renal function.

The risk of the lowest quartile of measured 24-h urinary Na excretion (<104.2 mEq/day) was not significantly higher than that of the second quartile of urinary Na excretion in this study. One study showed a significant association between low urinary Na excretion and incidence of ESRD in Type 1 DM [41]. Salt reduction contributed to increased RAS activity, increased sympathetic activity and increased insulin resistance. All of these changes are also risk factors of diabetic complications [42–45]. In the general population, a U-shaped association was identified

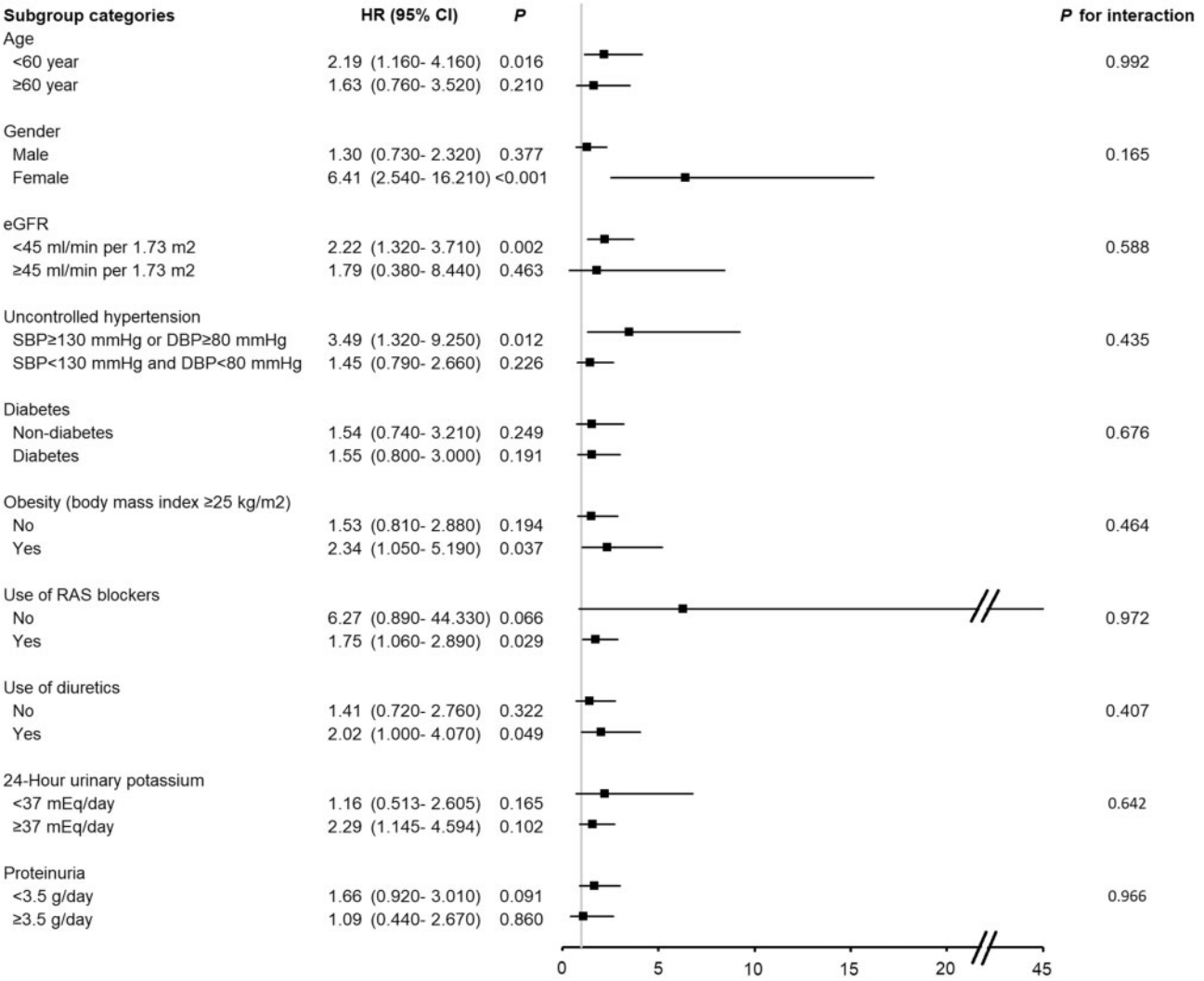

FIGURE 2: Subgroup analysis for the association of measured 24-h urinary sodium excretion with CKD progression. CI, confidence interval.

between daily salt intake and CKD development, which was defined as either eGFR <60 mL/min/1.73 m^2 or as development of proteinuria only when HTN was present [22]. These results also demonstrated an increased risk of poor renal outcome from very low salt intake. However, these data were limited to subjects with Type 1 DM or HTN. Therefore, these results might differ from those of the entire CKD population.

The increased risk of poor renal outcome from high salt intake was most pronounced in patients <60 years of age. The association between high salt intake and risk of poor renal outcome increased in subjects with HTN <60 years [22]. The activity of RAS was higher in young adults than it was in older people [46]. High RAS activity promoted vasoconstriction, cell proliferation and sympathetic activity [47], all of which could contribute to CKD progression.

In this study, urinary Na excretion was particularly associated with increased risk of renal outcome in women. Because of the differential effects of estrogen and testosterone on RAS, there may be sex differences in blood pressure [48]. Compared with estrogen, testosterone has a greater effect on angiotensin-converting enzyme (ACE) activity [49]. Because androgen deficiency develops in older men, post-andropausal men have low serum aminopeptidase A (APA) and ACE activities. Both APA and ACE are components of RAS. Inhibition of these enzymes could play a role as antihypertensive drugs. In our data, >60% of patients were post-andropausal men or post-menopausal women (aged ≥55 years). Post-menopausal women experience greater changes in blood pressure than do post-andropausal men [49, 50]. Therefore, the risk of renal dysfunction may be higher in the female group than in the male group. This was also observed in the general population. High salt intake was strongly associated with risk of CKD development in women ≥60 years old. CKD development was defined as eGFR <60 mL/min/1.73 m^2 or development of proteinuria [22]. Based on these data, we can infer why the risk of CKD progression was pronounced in the female subgroup compared with the male subgroup.

The strengths of this study include a large, homogeneous population. Our study included variable etiologies of CKD with eGFR <60 mL/min/1.73 m^2. Because information regarding measured 24-h urinary Na excretion was available for most subjects, it was possible to analyze the renal outcomes from a relatively large CKD population with long-term follow-up. Our sensitivity analysis using spot urine samples supported the primary analysis. This was the first Asian study to show an

association between high salt diet and CKD progression in CKD patients. Regardless, this study also has several limitations. It was an observational study of Korean CKD patients. The nutritional status evaluation such as food diary or food frequency questionnaire was not performed. In addition, dietary salt intake was based on a single measurement of 24-h urinary Na excretion at baseline. However, in the sensitivity analysis (that used estimated 24-h urinary Na excretion from spot urine sodium), the highest salt intake was also associated with risk of composite renal outcome.

In conclusion, high salt intake is associated with increased risk of CKD progression in CKD patients. In particular, risk was most pronounced in patients <60 years old or in women. Our findings suggest that urinary Na excretion is a predictor of CKD progression.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

FUNDING

This research was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (grants 2011E3300300, 2012E3301100, 2013E3301600, 2013E3301601, 2013E3301602, 2016E3300200 and 2016E3300201). The funders had no role in study design, data collection or analysis, decision to publish or preparation of the manuscript.

AUTHORS' CONTRIBUTIONS

The specific contribution of each author is as follows. M.K. and K.-H.O. designed the study. M.K. analyzed and interpreted the results and drafted the manuscript. E.K., H.R., S.K.P., Y.Y.H. and Y.H. analyzed and interpreted the data. J.K. advised and assisted in the statistical analysis. E.K., H.R., S.A.S. and S.W.K. reviewed and edited the manuscript. T.-H.Y., S.S.H. and C.A. conceived the study and assisted in the analyses. K.-H.O. conceived the study, analyzed the results, interpreted the data and reviewed the manuscript. All of the authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Minutolo *et al.* Sodium intake and progression of chronic kidney disease—has the time finally come to do the impossible: a prospective randomized controlled trial? *Nephrol Dial Transplant* 2021; 36: 381–384)

REFERENCES

1. Snelson M, Clarke RE, Coughlan MT. Stirring the pot: can dietary modification alleviate the burden of CKD? *Nutrients* 2017; 9: 265
2. Collins AJ, Foley RN, Gilbertson DT *et al.* United States Renal Data System public health surveillance of chronic kidney disease and end-stage renal disease. *Kidney Int Suppl* 2015; 5: 2–7
3. Jha V, Garcia-Garcia G, Iseki K *et al.* Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; 382: 260–272
4. Jin DC, Yun SR, Lee SW *et al.* Lessons from 30 years' data of Korean end-stage renal disease registry, 1985-2015. *Kidney Res Clin Pract* 2015; 34: 132–139
5. de Borst MH, Navis G. Sodium intake, RAAS-blockade and progressive renal disease. *Pharmacol Res* 2016; 107: 344–351
6. Powles J, Fahimi S, Micha R *et al.*; on behalf of the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE). Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open* 2013; 3: e003733
7. Aburto NJ, Ziolkovska A, Hooper L *et al.* Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013; 346: f1326
8. Cook NR, Cutler JA, Obarzanek E *et al.* Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007; 334: 885–888
9. He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* 2009; 23: 363–384
10. Hong JW, Noh JH, Kim DJ. Factors associated with high sodium intake based on estimated 24-hour urinary sodium excretion: the 2009–2011 Korea National Health and Nutrition Examination Survey. *Medicine (Baltimore)* 2016; 95: e2864
11. Joshi SR, Mohan V, Joshi SS *et al.* Transcultural diabetes nutrition therapy algorithm: the Asian Indian application. *Curr Diab Rep* 2012; 12: 204–212
12. Manyanga T, Tremblay MS, Chaput JP *et al.*; for the ISCOLE Research Group. Socioeconomic status and dietary patterns in children from around the world: different associations by levels of country human development? *BMC Public Health* 2017; 17: 457
13. Mora N, Golden SH. Understanding cultural influences on dietary habits in Asian, Middle Eastern, and Latino patients with type 2 diabetes: a review of current literature and future directions. *Curr Diab Rep* 2017; 17: 126
14. Inker LA, Astor BC, Fox CH *et al.* KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014; 63: 713–735
15. Jones-Burton C, Mishra SI, Fink JC *et al.* An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *Am J Nephrol* 2006; 26: 268–275
16. Swift PA, Markandu ND, Sagnella GA *et al.* Modest salt reduction reduces blood pressure and urine protein excretion in black hypertensives: a randomized control trial. *Hypertension* 2005; 46: 308–312
17. He J, Mills KT, Appel LJ *et al.*; for the Chronic Renal Insufficiency Cohort Study Investigators. Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol* 2016; 27: 1202–1212
18. Vegter S, Perna A, Postma MJ *et al.* Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol* 2012; 23: 165–173
19. Lambers Heerspink HJ, Holtkamp FA, Parving HH *et al.* Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int* 2012; 82: 330–337
20. Fan L, Tighiouart H, Levey AS *et al.* Urinary sodium excretion and kidney failure in nondiabetic chronic kidney disease. *Kidney Int* 2014; 86: 582–588
21. Mazarova A, Molnar AO, Akbari A *et al.* The association of urinary sodium excretion and the need for renal replacement therapy in advanced chronic kidney disease: a cohort study. *BMC Nephrol* 2016; 17: 123
22. Yoon CY, Noh J, Lee J *et al.* High and low sodium intakes are associated with incident chronic kidney disease in patients with normal renal function and hypertension. *Kidney Int* 2018; 93: 921–931
23. Oh KH, Park SK, Park HC *et al.*; Representing KNOW-CKD Study Group. KNOW-CKD (KoreaN cohort study for outcome in patients with chronic kidney disease): design and methods. *BMC Nephrol* 2014; 15: 80
24. Kang E, Han M, Kim H *et al.* Baseline general characteristics of the Korean chronic kidney disease: report from the KoreaN Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD). *J Korean Med Sci* 2017; 32: 221–230
25. McLean RM. Measuring population sodium intake: a review of methods. *Nutrients* 2014; 6: 4651–4662
26. Whitton C, Gay GM, Lim RB *et al.* Evaluation of equations for predicting 24-hour urinary sodium excretion from casual urine samples in Asian adults. *J Nutr* 2016; 146: 1609–1615
27. Levey AS, Stevens LA, Schmid CH *et al.*; for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612

28. Whelton PK, Carey RM, Aronow WS *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Hypertension* 2018; 71: e13–e115
29. Maroni BJ, Steinman TI, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 1985; 27: 58–65
30. Rand WM, Pellett PL, Young VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. *Am J Clin Nutr* 2003; 77: 109–127
31. Ahn SY, Kim DK, Park JH *et al.* Long-term effects of intensive low-salt diet education on deterioration of glomerular filtration rate among non-diabetic hypertensive patients with chronic kidney disease. *Kidney Blood Press Res* 2019; 44: 1101–1114
32. Kim IY, Song SH. Blood pressure measurement in patients with chronic kidney disease: from clinical trial to clinical practice. *Kidney Res Clin Pract* 2019; 38: 138–140
33. Peterson JC, Adler S, Burkart JM *et al.* Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995; 123: 754–762
34. Mente A, O'Donnell MJ, Rangarajan S *et al.* Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med* 2014; 371: 601–611
35. McMahon EJ, Bauer JD, Hawley CM *et al.* A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 2013; 24: 2096–2103
36. Midgley JP, Matthew AG, Greenwood CM *et al.* Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; 275: 1590–1597
37. Cao W, Li A, Wang L *et al.* A salt-induced reno-cerebral reflex activates renin-angiotensin systems and promotes CKD progression. *J Am Soc Nephrol* 2015; 26: 1619–1633
38. Kwakernaak AJ, Waanders F, Slagman MC *et al.* Sodium restriction on top of renin-angiotensin-aldosterone system blockade increases circulating levels of N-acetyl-seryl-aspartyl-lysyl-proline in chronic kidney disease patients. *J Hypertens* 2013; 31: 2425–2432
39. Al-Solaiman Y, Jesri A, Zhao Y *et al.* Low-sodium DASH reduces oxidative stress and improves vascular function in salt-sensitive humans. *J Hum Hypertens* 2009; 23: 826–835
40. Todd AS, Macginley RJ, Schollum JB *et al.* Dietary salt loading impairs arterial vascular reactivity. *Am J Clin Nutr* 2010; 91: 557–564
41. Thomas MC, Moran J, Forsblom C *et al.*; for the FinnDiane Study Group. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care* 2011; 34: 861–866
42. Grassi G, Dell'Oro R, Seravalle G *et al.* Short- and long-term neuroadrenergic effects of moderate dietary sodium restriction in essential hypertension. *Circulation* 2002; 106: 1957–1961
43. Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA* 1998; 279: 1383–1391
44. Petrie JR, Morris AD, Minamisawa K *et al.* Dietary sodium restriction impairs insulin sensitivity in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1998; 83: 1552–1557
45. Garg R, Williams GH, Hurwitz S *et al.* Low-salt diet increases insulin resistance in healthy subjects. *Metabolism* 2011; 60: 965–968
46. Bauer JH. Age-related changes in the renin-aldosterone system. Physiological effects and clinical implications. *Drugs Aging* 1993; 3: 238–245
47. Malik U, Raizada V. Some aspects of the renin-angiotensin-system in hemodialysis patients. *Kidney Blood Press Res* 2015; 40: 614–622
48. Maric-Bilkan C, Manigrasso MB. Sex differences in hypertension: contribution of the renin-angiotensin system. *Gend Med* 2012; 9: 287–291
49. Fernandez-Atucha A, Izagirre A, Fraile-Bermudez AB *et al.* Sex differences in the aging pattern of renin-angiotensin system serum peptidases. *Biol Sex Differ* 2017; 8: 5
50. Reaux-Le Goazigo A, Iturrioz X, Fassot C *et al.* Role of angiotensin III in hypertension. *Curr Hypertens Rep* 2005; 7: 128–134

Received: 4.12.2019; Editorial decision: 7.4.2020

Nephrol Dial Transplant (2021) 36: 519–528
doi: 10.1093/ndt/gfaa128
Advance Access publication 8 June 2020

Identifying key predictors of mortality in young patients on chronic haemodialysis—a machine learning approach

Verena Gotta [1,*], Georgi Tancev[2,*], Olivera Marsenic[3], Julia E. Vogt[4,†] and Marc Pfister[1,5]

[1]Pediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel, Switzerland, [2]Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland, [3]Pediatric Nephrology, Stanford University School of Medicine, Lucile Packard Children's Hospital, Stanford, CA, USA, [4]Department of Computer Science, ETH Zurich, Zurich, Switzerland and [5]Certara, Princeton, NJ, USA

*Shared first authors, †Shared last authors Correspondence to: Verena Gotta; E-mail: verena.gotta@ukbb.ch

ABSTRACT

Background. The mortality risk remains significant in paediatric and adult patients on chronic haemodialysis (HD) treatment. We aimed to identify factors associated with mortality in patients who started HD as children and continued HD as adults.

Methods. The data originated from a cohort of patients <30 years of age who started HD in childhood (≤19 years) on thrice-weekly HD in outpatient DaVita dialysis centres between 2004 and 2016. Patients with at least 5 years of follow-up since the initiation of HD or death within 5 years were included; 105 variables relating to demographics, HD treatment and laboratory measurements were evaluated as predictors of 5-year mortality utilizing a machine learning approach (random forest).