Clinical Kidney Journal, 2024, vol. 17, no. 8, sfae137

https://doi.org/10.1093/ckj/sfae137
Advance Access Publication Date: 13 May 2024
Original Article

ORIGINAL ARTICLE

Inverse association between serum chloride levels and the risk of atrial fibrillation in chronic kidney disease patients

Yangang Gan [1,*], Sheng Nie [2,*], Mingzhen Pang[2], Rong Huang[1], Hong Xu [3], Bicheng Liu [4], Jianping Weng[5], Chen Chunbo [6], Huafeng Liu[7], Hua Li[8], Yaozhong Kong[9], Guisen Li[10], Qijun Wan [11], Yan Zha[12], Ying Hu[13], Gang Xu[14], Yongjun Shi[15], Yilun Zhou[16], Guobin Su[17], Ying Tang[18], Mengchun Gong[19,20], Fan Fan Hou[2] and Qiongqiong Yang[1]

[1]Department of Nephrology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China, [2]Division of Nephrology, Nanfang Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease; State Key Laboratory of Organ Failure Research; Guangdong Provincial Institute of Nephrology; Guangdong Provincial Key Laboratory of Renal Failure Research, Guangzhou, China, [3]Children's Hospital of Fudan University, Shanghai, China, [4]Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing, China, [5]Department of Endocrinology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China, [6]Department of Critical Care Medicine, Maoming People's Hospital, Maoming, China, [7]Key Laboratory of Prevention and Management of Chronic Kidney Disease of Zhanjiang City, Institute of Nephrology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, China, [8]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China, [9]Department of Nephrology, the First People's Hospital of Foshan, Foshan, Guangdong, China, [10]Renal Department and Institute of Nephrology, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Sichuan Clinical Research Center for Kidney Diseases, Chengdu, China, [11]The Second People's Hospital of Shenzhen, Shenzhen University, Shenzhen, China, [12]Guizhou Provincial People's Hospital, Guizhou University, Guiyang, China, [13]The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China, [14]Division of Nephrology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [15]Huizhou Municipal Central Hospital, Sun Yat-Sen University, Huizhou, China, [16]Department of Nephrology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China, [17]Department of Nephrology, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital, The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, China, [18]The Third Affiliated Hospital of Southern Medical University, Guangzhou, China, [19]Institute of Health Management, Southern Medical University, Guangzhou, China and [20]Digital Health China Technologies Co. Ltd., Beijing, China

*These authors contributed equally.
Correspondence to: Qiongqiong Yang; E-mail: yangqq@mail.sysu.edu.cn; Fan Fan Hou; E-mail: ffhouguangzhou@163.com

Received: 5.11.2023; Editorial decision: 11.4.2024

ABSTRACT

Background. Electrolyte abnormalities are common symptoms of chronic kidney disease (CKD), but previous studies have mainly focussed on serum potassium and sodium levels. Chloride is an important biomarker for the prognosis of various diseases. However, the relationship between serum chloride levels and atrial fibrillation (AF) in CKD patients is unclear.

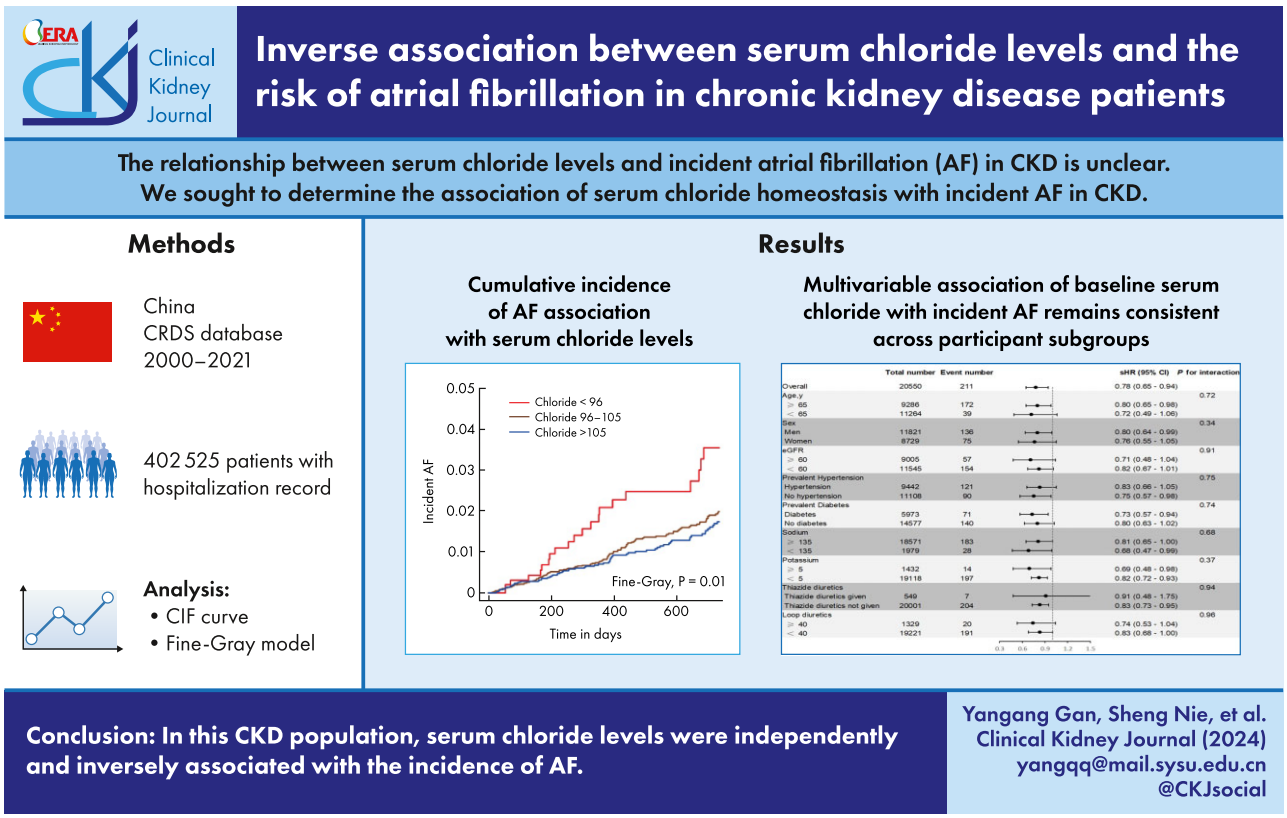
Objective. In this study, we sought to determine the association between serum chloride homeostasis and AF in CKD patients.

Methods. In this retrospective cohort study, we included patients who met the diagnostic criteria for CKD in China between 2000 and 2021. Competing risk regression for AF was performed. The associations of the baseline serum chloride concentration with heart failure (HF) and stroke incidence were also calculated by competing risk regression. The association of baseline serum chloride levels with all-cause death was determined by a Cox regression model.

Results. The study cohort comprised 20 550 participants. During a median follow-up of 350 days (interquartile range, 123–730 days), 211 of the 20 550 CKD patients developed AF. After multivariable adjustment, every decrease in the standard deviation of serum chloride (5.02 mmol/l) was associated with a high risk for AF [sub-hazard ratio (sHR) 0.78, 95% confidence interval (CI) 0.65–0.94, $P = .008$]. These results were also consistent with those of the stratified and sensitivity analyses. According to the fully adjusted models, the serum chloride concentration was also associated with a high risk for incident HF (sHR 0.85, 95% CI 0.80–0.91, $P < .001$), a high risk for incident stroke (sHR 0.87, 95% CI 0.81–0.94, $P < .001$), and a high risk for all-cause death [hazard ratio (HR) 0.82, 95% CI 0.73–0.91, $P < .001$].

Conclusion. In this CKD population, serum chloride levels were independently and inversely associated with the incidence of AF. Lower serum chloride levels were also associated with an increased risk of incident HF, stroke, and all-cause death.

GRAPHICAL ABSTRACT



Keywords: atrial fibrillation, chronic kidney disease, electrolyte imbalances, serum chloride

INTRODUCTION

Chronic kidney disease (CKD) is a vitally important public health problem worldwide [1]. The global prevalence of CKD is ∼13.4% (11.7%–15.1%) [2]. Kidney disease is an important risk factor for cardiovascular disease [3], which is the leading cause of death in CKD patients [4]. Atrial fibrillation (AF) is a common arrhythmia in the general population and is associated with the incidence of cardiovascular events and death [5]. In adults, the prevalence rate of AF is ∼2%–4% [6]. Studies from a multicentre adult population in the USA have shown that ∼15%–20% of patients with CKD develop AF [7–9]. The incidence of AF in CKD patients is associated with decreased renal function. However, the reason for the high incidence of AF in CKD patients is still unclear [10].

Electrolyte disturbances are common complications in the CKD population [1]. Sodium and potassium levels, which are strong predictors of CKD, have been studied widely [11–14]. In studies on a variety of diseases, hyponatraemia [15, 16] and hypokalaemia or hyperkalaemia have been shown to be markers of a poor prognosis [14, 17]. One study showed that decreased serum chloride concentrations among people with chronic heart failure (HF) are associated with a high risk of death [18]. In addition, low serum chloride levels in patients with HFpEF were independently related to cardiovascular and all-cause death [19], independent of serum sodium and bicarbonate concentrations. These studies revealed that serum chloride plays a key role in cardiovascular disease and death. However, the role of serum chloride homeostasis in the incidence of AF, especially in CKD patients, is unclear. Therefore, we aimed to explore the association between serum chloride concentration and incident AF in CKD patients. We also explored the association of serum chloride with HF, stroke, and all-cause death. This study provides a reference for the clinical prevention and treatment of electrolyte disturbances in patients with CKD.

MATERIALS AND METHODS

Study population

The data of the participants in this study were collected from the China Renal Data System (CRDS). The CRDS, a cooperative network, includes 19 regional medical centres in China to facilitate clinical research on kidney disease [20–22]. The clinical data included admission and discharge dates, division of each hospitalization, diagnosis codes, laboratory assay results, imaging and histological reports, prescriptions, and medical records of both inpatient and outpatient visits. This study cohort included 20 550 patients with CKD diagnosed according to the K/DOQI guidelines [23] who were aged ≥18 years and admitted between 2000 and 2021; those receiving haemodialysis, peritoneal dialysis, or renal transplantation, and those with HF, valvular heart disease, primary hypertrophic cardiomyopathy, stroke, acute coronary syndrome, and previously documented AF were excluded. Patients lacking serum creatinine and chloride levels and 12-lead resting electrocardiogram (ECG) data were also excluded. For patients with multiple hospitalizations, the first hospitalization after CKD diagnosis was regarded as the baseline analysis set. The ethics committees of the participating centres approved the protocol of this study and waived patients' informed consent. This study complies with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines [24].

Data collection and measurements

The baseline data collected included demographic information, medical history, medication lists, blood pressure measurements, and body measurements. Self-report questionnaires were used to assess cardiovascular disease history, including hypertension, diabetes, coronary artery disease, valvular heart disease, primary hypertrophic cardiomyopathy, HF, stroke, and peripheral vascular disease. Blood samples were analysed for comprehensive metabolic panels, and the eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation [25].

Exposure and outcomes

The primary exposure was baseline serum chloride levels, which were measured at baseline in 20 550 participants. The main outcome was incident AF diagnosed between cohort entry (2000) and 2021. According to a previously described approach, incident AF was defined by the first diagnosis of AF or ≥2 ambulatory visits for AF on the basis of ECG [26–28]. We also assessed the AF-related outcomes after baseline in the diagnosis position: HF, stroke, and all-cause death. All participants were followed up until death, loss to follow-up, or 2021.

Statistical analysis

Descriptive statistics are summarized as the mean ± standard deviation (SD) or median and interquartile range for continuous variables, and the frequency distribution is presented as a percentage for categorical variables. Groups based on serum chloride levels were compared with χ^2 tests for categorical variables and ANOVA or Kruskal–Wallis tests for normally or non-normally distributed continuous variables, respectively. We assessed the association between serum chloride levels and the risk of AF by evaluating serum chloride levels as a continuous variable (per 1 SD increase) and as a categorical variable (the normochloraemia group was the reference group). Cumulative incidence curves for AF, HF, stroke, and all-cause death in relation to baseline serum chloride levels were evaluated. We used Fine–Gray competing risk models to investigate the unadjusted and multivariable-adjusted associations of serum chloride with AF, HF, and stroke. A Cox proportional hazards regression model was used to investigate the unadjusted and multivariable-adjusted associations between serum chloride concentration and all-cause death. We fitted a series of hierarchically adjusted models as follows: (i) Model 1 (unadjusted); (ii) Model 2 was stratified by site and included age, sex, body mass index (BMI), albumin, haemoglobin, total cholesterol, triglyceride, eGFR, calcium, phosphorus, sodium, potassium, N-terminal pro-brain natriuretic peptide (NT-proBNP), hypertension, diabetes, coronary artery disease, peripheral vascular disease, and history of medications (renin–angiotensin system blockers, loop diuretics, thiazide diuretics, calcium channel blockers, β-blockers, statins, and aspirin). We examined the possible nonlinear relationship between serum chloride levels and clinical outcomes with restricted cubic splines. Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and quartic-spline terms [29]. Subgroup analyses were also performed, stratifying by predefined variables: age [<65, ≥65 years], sex, eGFR [<60, ≥60 ml/min/1.73 m^2], sodium [<135, ≥135 mmol/l], potassium [<5, ≥5 mmol/l], the

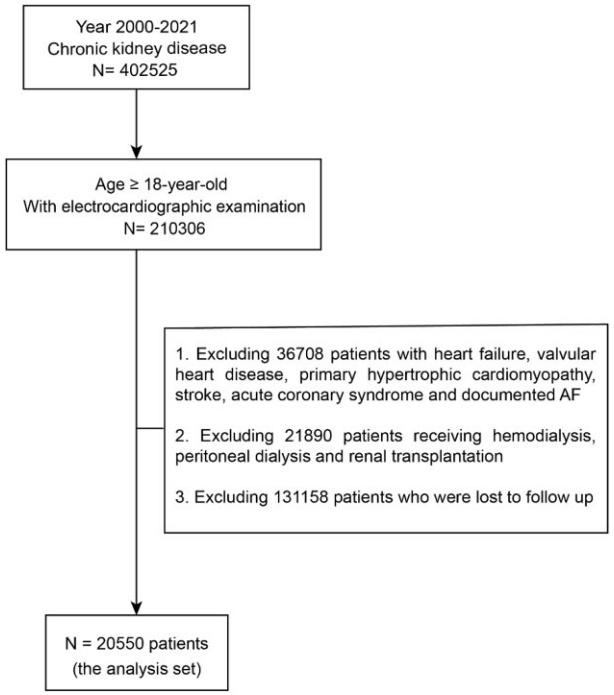


Figure 1: Flow chart of the study population selection process.

presence/absence of diabetes and hypertension and the use of diuretic drugs. An interaction term was added to the Fine–Gray hazards regression model to test for possible effect modification by the grouping factors. All analyses were conducted using R v.4.1.0; a two-sided *P* value of <.05 was considered to indicate statistical significance for all analyses.

RESULTS

Baseline characteristics

The final analysis cohort included a total of 20550 participants (Fig. 1). In our study cohort, the baseline chloride concentration was normally distributed, with median and mean baseline chloride levels of 104.6 (101.6–107.3) and 104.26 ± 5.02 mmol/l, respectively. The prevalence rate of hypochloraemia (≤96 mmol/l) was 5.3%. The participants in this study had a mean age of 60.94 (16.53) years, and 57.5% were male. The group with lower chloride levels had lower eGFR levels and a higher prevalence of diabetes and peripheral vascular disease, along with a significantly higher use of loop diuretics and aspirin. The baseline characteristics across baseline serum chloride levels are shown in Table 1.

Chloride levels and clinical outcomes

During a median follow-up of 350 days, 211 (1.03%) patients developed AF. Over the same period, there were 1539 HF (7.49%), 1247 stroke (6.07%), and 510 all-cause deaths (2.48%). The

Table 1: Baseline characteristics according to chloride concentration

	Chloride			
Variable[a]	<96 mmol/l (*n* = 1093)	96–105 mmol/l (*n* = 11718)	>105 mmol/l (*n* = 7739)	*P* value
Age (years)	62.40 (16.12)	60.85 (16.59)	60.87 (16.49)	.011
Female patients, *n* (%)	454 (41.5)	4771 (40.7)	3504 (45.3)	<.001
BMI (kg/m^2)	22.38 (3.93)	23.36 (3.86)	23.39 (3.68)	<.001
SBP (mmHg)	134.90 (24.41)	137.94 (23.45)	140.13 (23.87)	<.001
DBP (mmHg)	80.16 (15.19)	81.82 (14.12)	81.80 (14.43)	.001
Albumin (g/l)	35.04 (6.76)	37.08 (6.49)	34.57 (7.30)	<.001
Haemoglobin (g/l)	114.67 (25.80)	120.28 (24.45)	111.52 (24.81)	<.001
Total cholesterol (mmol/l)	4.49 (1.44)	4.76 (1.38)	4.77 (1.52)	<.001
Triglyceride (mmol/l)	1.73 (1.27)	1.77 (1.24)	1.69 (1.16)	<.001
Creatinine (μmol/l)	116 (80.7–237)	101 (73–147)	117 (83–199.75)	<.001
eGFR (ml/min/1.73 m^2)	51.5 (34.76)	62.64 (33.66)	53.8 (33.2)	<.001
Calcium (mmol/l)	2.21 (0.23)	2.23 (0.18)	2.17 (0.19)	<.001
Phosphorus (mmol/l)	1.3 (0.54)	1.22 (0.33)	1.24 (0.32)	<.001
Sodium (mmol/l)	132.1 (5.49)	139.15 (3.25)	141.5 (2.98)	<.001
Potassium (mmol/l)	4.05 (0.76)	4.05 (0.56)	4.15 (0.61)	<.001
NT-proBNP (pg/ml)	74.9 (32.1, 216)	63.4 (28.2, 164)	76.2 (31.9, 208.9)	<.001
Hypertension, *n* (%)	471 (43.1)	5351 (45.7)	3620 (46.8)	.047
Diabetes, *n* (%)	471 (43.1)	3664 (31.3)	1838 (23.7)	<.001
Coronary heart disease, *n* (%)	137 (12.5)	1547 (13.2)	914 (11.8)	.017
Peripheral vascular disease, *n* (%)	239 (21.9)	2309 (19.7)	1341 (17.3)	<.001
RASBs, *n* (%)	87 (8)	905 (7.7)	619 (8)	.770
Loop diuretics, *n* (%)	282 (25.8)	2155 (18.4)	1812 (23.4)	<.001
Loop diuretic dose (mg, furosemide equivalents)	20 (20, 40)	20 (20, 40)	20 (20, 40)	.170
Thiazide diuretics, *n* (%)	33 (3)	265 (2.3)	251 (3.2)	<.001
CCBs, *n* (%)	302 (27.6)	3349 (28.6)	2635 (34)	<.001
β-blockers, *n* (%)	169 (15.5)	1653 (14.1)	1207 (15.6)	.013
Statins, *n* (%)	179 (16.4)	1969 (16.8)	1278 (16.5)	.840
Aspirin, *n* (%)	134 (12.3)	1377 (11.8)	818 (10.6)	.024

[a]The results are presented as the means ± SDs, interquartile ranges or numbers (percentages) for categorical variables.
SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; RASBs, renin–angiotensin system blockers; CCBs, calcium channel blockers.

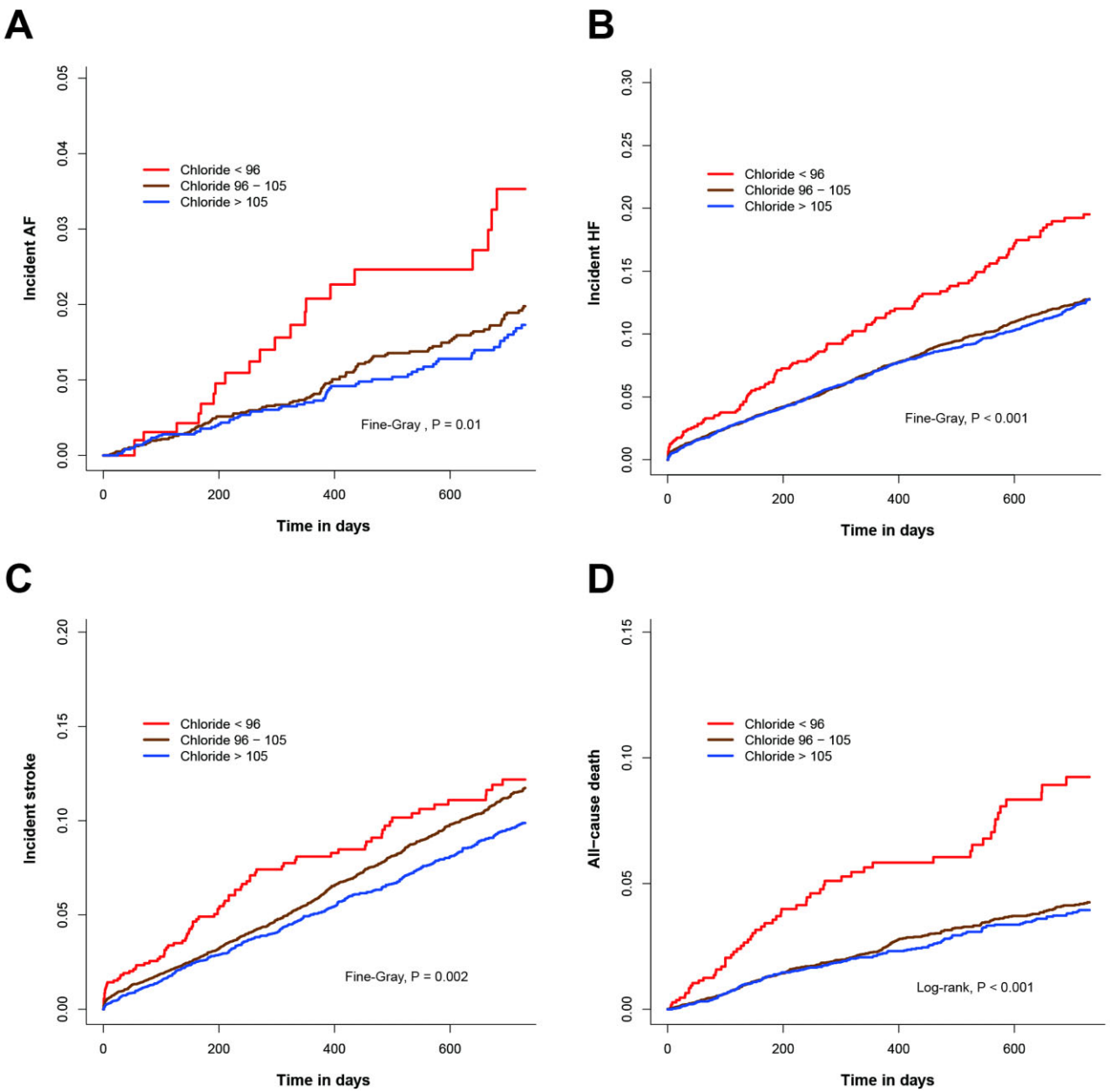


Figure 2: Cumulative incidence curves for AF (A), HF (B), stroke (C), and all-cause death (D) in relation to baseline serum chloride levels.

cumulative incidences of AF, HF, stroke, and all-cause death are shown in Fig. 2. In restricted cubic splines, we observed a negative linear relationship between chloride levels and the incidence of AF, HF, stroke, and all-cause death (Fig. 3). After multivariable adjustment, the association between serum chloride levels and incident AF remained significant and inversely proportional [sub-hazard ratio (sHR), per SD: 0.78; 95% CI: 0.65 to 0.94; $P = .008$] shown in Table 2. Adjusting for various factors, including demographic variables, comorbid conditions, medications, and laboratory data, slightly attenuated the relationship between the baseline serum chloride concentration and subsequent AF.

Next, we further explored the effects of chloride on HF and stroke. In competing regression analysis, serum chloride levels were associated with the risk of HF (sHR, per SD: 0.85; 95% CI: 0.80 to 0.91; $P < .001$) and the risk of stroke (sHR, per SD: 0.87; 95% CI: 0.81 to 0.94; $P < .001$) according to the multivariable adjustment model shown in Table 2. Finally, Cox proportional hazards models were used to explore the association between serum chloride concentration and all-cause death, as shown in Table 3. Serum chloride levels were associated with the risk of all-cause death [hazard ratio (HR), per SD: 0.82; 95% CI: 0.73–0.91, $P < .001$] according to the multivariable adjustment model.

Analyses were stratified across different participant subgroups

We conducted a comprehensive analysis to assess the relationship between baseline serum chloride levels and the risk of AF, considering various participant subgroups. These subgroups were stratified on the basis of age, sex, eGFR, prevalent hypertension, prevalent diabetes, sodium, potassium, and the use of

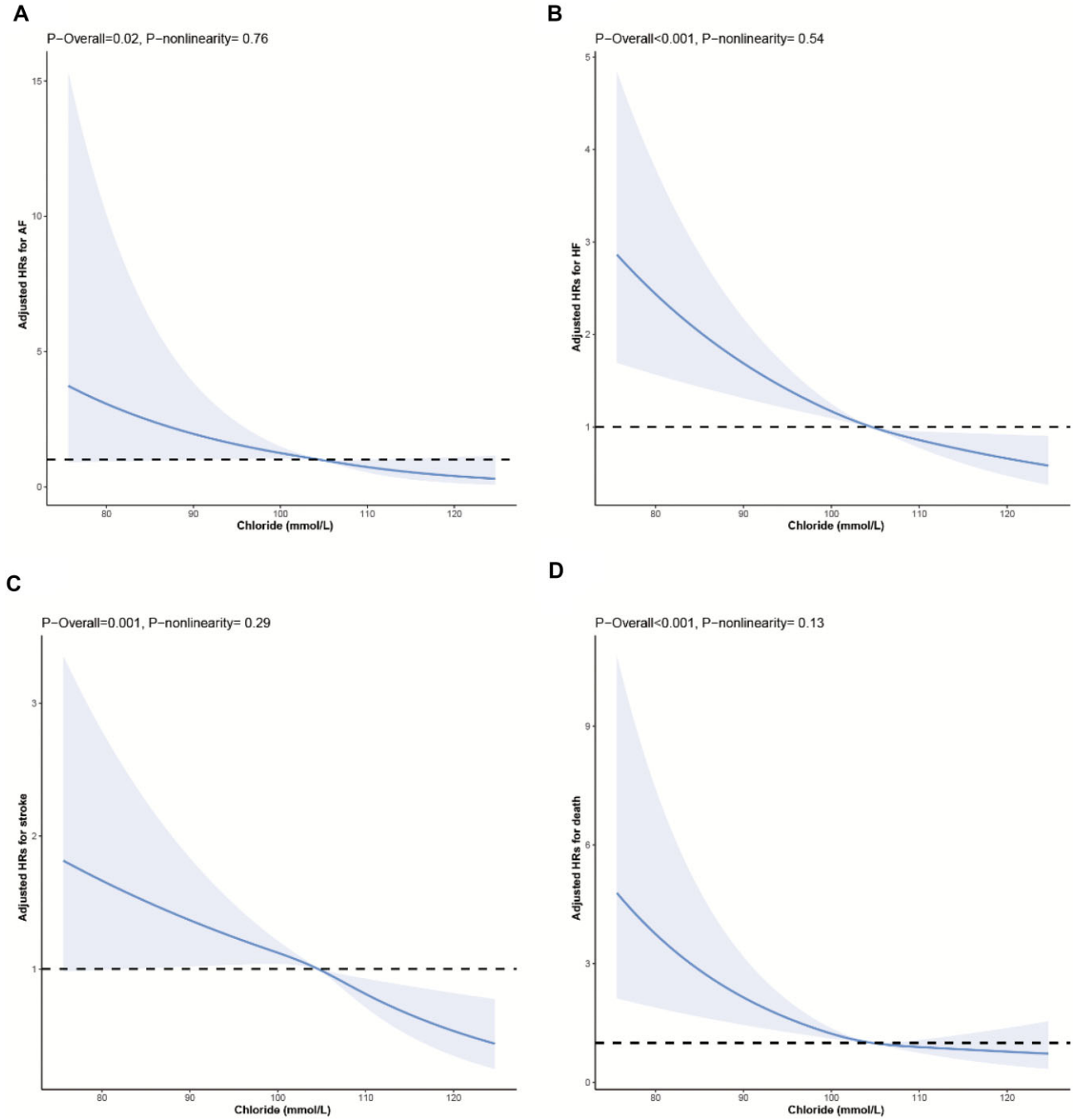


Figure 3: Association between baseline serum chloride levels and clinical outcomes. After we adjusted for demographic variables, comorbid conditions, medications, and laboratory data, a restricted cubic spline model was generated according to baseline serum chloride levels. Adjusted HRs for (A) AF, (B) HF, (C) stroke, and (D) all-cause death.

diuretic drugs. The findings revealed that the association between baseline serum chloride and incident AF was consistent across all subgroups, although some subgroup analyses had wide confidence intervals (Fig. 4).

Sensitivity analyses

When we repeated the main analysis while excluding individuals who developed AF within 3 months after serum chloride testing, the association between baseline serum chloride levels and incident AF remained qualitatively unchanged. The sHR per SD increase in serum chloride was 0.76 (95% CI: 0.62–0.94). Furthermore, excluding other baseline arrhythmias still showed an inverse association between serum chloride and incident AF, with a sHR per SD of 0.74 (95% CI: 0.60–0.90).

DISCUSSION

In this study, we explored the importance of serum chloride homeostasis for incident AF in CKD patients. There are two key

Table 2: Fine–Gray competing models for the association of chloride levels with incident AF, HF and stroke accounting for competing risk of death

Chloride	Cases/Total, No.	sHR (95%CI) Model 1[a]	*P* value	sHR (95%CI) Model 2[b]	*P* value
AF					
Continuous (SD)	211/20550	0.84 (0.74–0.95)	.006	0.78 (0.65–0.94)	.008
Categorical					
Chloride <96	21/1093	1.83 (1.15–2.92)	.010	1.85 (1.06–3.23)	.032
Chloride 96–105	121/11718	Ref		Ref	
Chloride ≥105	69/7739	0.87 (0.65–1.17)	.360	0.81 (0.58–1.14)	.220
HF					
Continuous (SD)	1539/20550	0.92 (0.87–0.97)	.003	0.85 (0.80–0.91)	<.001
Categorical					
Chloride <96	126/1093	1.60 (1.32–1.93)	<.001	1.45 (1.16–1.8)	.001
Chloride 96–105	855/11718	Ref		Ref	
Chloride ≥105	558/7739	0.98 (0.89–1.09)	.770	0. 80 (0.71–0.90)	<.001
Stroke					
Continuous (SD)	1247/20550	0.87 (0.82–0.92)	<.001	0.87 (0.81–0.94)	<.001
Categorical					
Chloride <96	84/1093	1.20 (0.95–1.51)	.120	1.08 (0.83–1.40)	.560
Chloride 96–105	750/11718	Ref		Ref	
Chloride ≥105	413/7739	0.84 (0.74–0.95)	.004	0.89 (0.77–1.01)	0.074

[a]Model 1: unadjusted.
[b]Model 2: adjusted for age, sex, BMI, albumin, haemoglobin, total cholesterol, triglycerides, eGFR, NT-proBNP, calcium, phosphorus, sodium, potassium, hypertension, diabetes, coronary artery disease, peripheral vascular disease, RASBs, loop diuretics, thiazide diuretics, CCBs, β blockers, statins, and aspirin.

Table 3: Cox regression models for the association between chloride levels and all-cause death

Chloride	Cases/Total No.	HR (95%CI) Model 1[a] †	*P* value	HR (95%CI) Model 2[b]	*P* value
Continuous (SD)	510/20550	0.80 (0.74–0.87)	<.001	0.82 (0.73–0.91)	<.001
Categorical					
Chloride < 96	59/1093	2.27 (1.72–3.01)	<.001	1.53 (1.1 -2.13)	.011
Chloride 96–105	281/11718	Ref		Ref	
Chloride ≥ 105	170/7739	0.93 (0.77–1.12)	.430	0.84 (0.68–1.04)	.110

[a]Model 1: unadjusted.
[b]Model 2: adjusted for age, sex, BMI, albumin, haemoglobin, total cholesterol, triglycerides, eGFR, NT-proBNP, calcium, phosphorus, sodium, potassium, hypertension, diabetes, coronary artery disease, peripheral vascular disease, RASB, loop diuretics, thiazide diuretics, CCB, β blocker, statins, and aspirin.

findings from this study of serum chloride in 20550 individuals with CKD. Baseline serum chloride levels were independently and inversely associated with incident AF in CKD patients. The associations between baseline serum chloride and incident AF were found to be independent of various factors, including sodium, potassium, calcium, phosphorus, medical history, and medications. These findings highlight the importance of serum chloride in patients with CKD and emphasize the need to investigate the underlying mechanisms through which low serum chloride levels affect the development of AF. A better understanding of these mechanisms could lead to the development of more effective preventive measures and treatment strategies for AF.

Much attention has been directed to sodium and potassium as strong predictors in CKD patients with and without ESRD [11–14]. However, serum chloride has not been included as a very important covariate in the analyses, despite the common use of serum chloride measurements in clinical practice in CKD patients. Chloride plays a crucial role in various homeostatic mechanisms, including the regulation of renin secretion [30], tubuloglomerular feedback [31, 32], blood pressure response [33], vascular inflammation [34], and altered acid–base homeostasis [35]. Serum chloride levels have been recognized as a predictor of adverse outcomes in different clinical scenarios. For instance, a population-based study by De Bacquer *et al*. demonstrated an association between low serum chloride levels and adverse outcomes [36]. In acute decompensated HF patients, low serum chloride was also found to be related to diuretic resistance and increased mortality [37, 38]. Additionally, low serum chloride levels were shown to be associated with an increased risk of in-hospital mortality following ischaemic stroke [39]. Furthermore, hypochloraemia has been associated with both all-cause and cardiovascular mortality in hypertensive patients [40].

There is also a study in which it was found that chloride ions have a dual effect on acute kidney injury (AKI) and are protective factors in patients with hypochloraemia [41]. Shintaro Mandai *et al*. discovered the prognostic impact of serum chloride levels among predialysis CKD patients [42]. Higher serum chloride levels in patients with CKD were associated with a decreased risk of eGFR decline, suggesting that it may serve as a useful biomarker for predicting CKD progression [43]. In this study, we also found that lower serum chloride levels were also associated with an increased risk of incident stroke, HF, and all-cause death. There

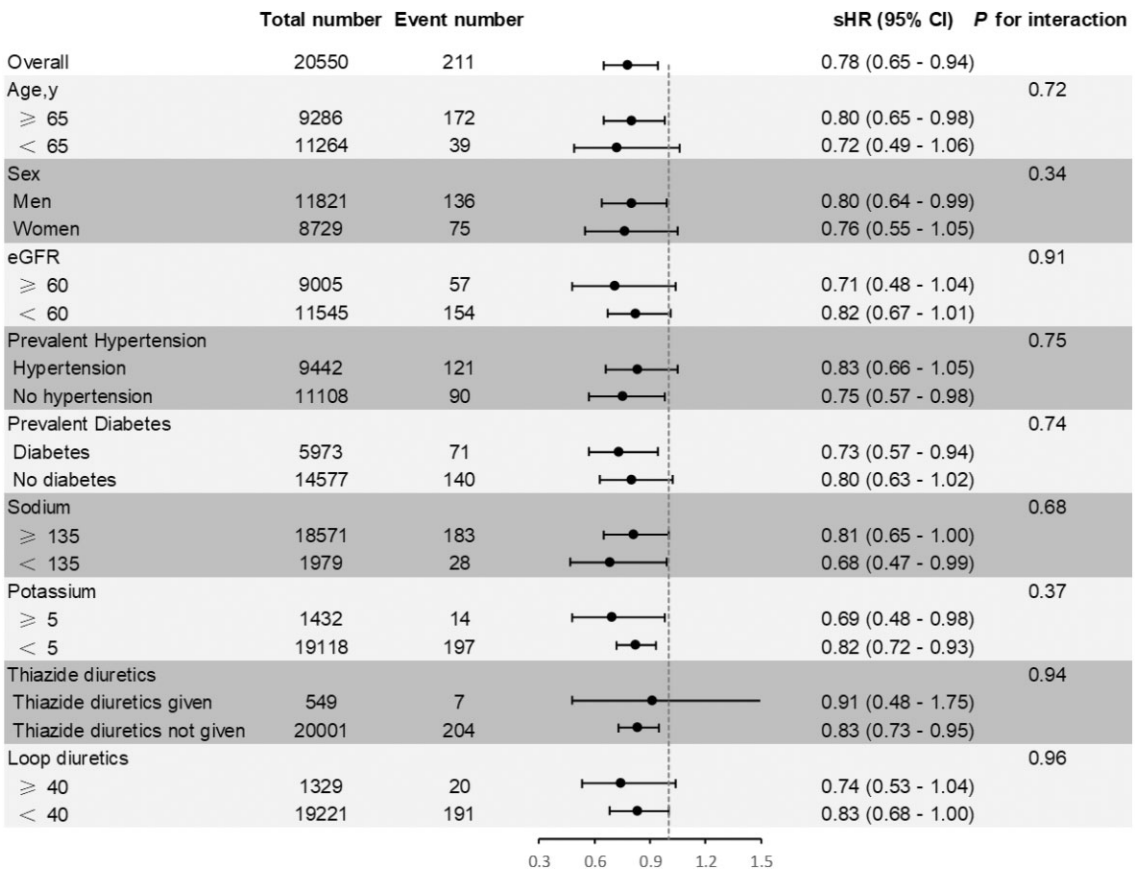


Figure 4: The multivariate association between baseline serum chloride concentration and incident AF was consistent across participant subgroups. The multivariate association between baseline serum chloride levels and incident AF was investigated across various participant subgroups. sHR; 95% CI, 95% confidence interval.

remain relatively few studies on chloride ions within the field of nephrology, indicating the need for increased attention and investigation.

AF is the most prevalent sustained arrhythmia in the general population, and its occurrence is particularly high among individuals with kidney disease. Among patients with ESRD undergoing dialysis, AF has been reported in 7%–20% of cases, which is two to three times higher than the rate in the general population [44–46]. Studies have also indicated a high incidence and prevalence of AF in nondialysis CKD patients [8, 9, 47]. Indeed, a meta-analysis of three cohorts demonstrated significant associations of a reduced eGFR and an increased urine albumin-to-creatinine ratio with an increased risk of AF [48]. CKD patients are susceptible to fluid and electrolyte imbalances, as well as metabolic acidosis, compared to individuals with normal renal function [49]. Hypokalaemia (serum potassium <3.5 mmol/l) has been linked to a higher risk of AF compared to normokalaemia [50]. Additionally, elevated circulating phosphorus has been associated with an increased risk of AF, while circulating calcium has not shown a significant association [51]. Interestingly, a community-based study observed a lower prevalence of AF in patients with higher chloride levels [52]. However, the relationship between serum chloride concentrations and the incidence of AF, especially in CKD patients, remains unclear. Our study contributes to the literature by demonstrating a connection between serum chloride levels and the occurrence of AF. Specifically, our findings suggest that CKD patients with lower serum chloride levels have a higher risk of developing AF. The group with lower chloride levels had lower eGFR levels and higher prevalence of diabetes and peripheral vascular disease, along with a significantly higher utilization of loop diuretics, which may partly explain the higher incidence of AF in this population. Indeed, low serum chloride levels may stimulate the activity of with-no-lysine kinases (WNKs) [53, 54], thereby enhancing the function of Na^+-K^+-$2Cl^-$ and Na^+-Cl^- cotransporters [55, 56]. These cotransporters play a crucial role in maintaining myocyte volume and pH homeostasis, which are essential for normal cardiac rhythm and contractility [57, 58]. Dysregulation of intracellular pH in myocytes is known to be arrhythmogenic [59] and impairs contractility [60]. Thus, abnormal chloride levels could affect cardiac rhythm and subsequently contribute to the development of AF. However, the precise mechanism by which serum chloride affects chloride channels or chloride-dependent cotransporters in humans remains unknown. Rigorously designed randomized controlled trials in CKD patients are needed to investigate whether chloride replacement could reduce the incidence of AF. Our study stands out due to several significant strengths. First, it features a substantial sample size, providing robust statistical power for analysis. Second, the inclusion of multiple centres across China enhances the diversity and representation of the study population. Furthermore, our study incorporates comprehensive data on potential major confounders, allowing for meticulous adjustment in the analysis. Considering these strengths, our study makes a unique contribution to the literature by reporting, for the first time, a retrospective association between baseline serum chloride levels and the incidence of AF in patients with CKD.

Limitations

There were several limitations to the present study. First, excluding patients without two follow-up visits may introduce selection bias, potentially compromising the representativeness of the study sample. Second, our study sample was selected from a population of patients with CKD in the CRDS who received follow-up care at one of the affiliated clinics. These patients might be sicker and have a higher rate of drug use than those who were not hospitalized and those who did not receive follow-up care at one of the affiliated clinics. Third, even after multivariable adjustment, residual confounding is always a concern. Fourth, the study's retrospective design raises concerns about selection bias and reliance on historical data, potentially affecting the accuracy and reliability of the results. Finally, patients covered by the CRDS were predominantly Chinese; whether there are ethnic differences in the influence of serum chloride on incident AF in patients with CKD warrants further research. Our findings need to be validated in other countries where guideline-based medical care is well documented.

CONCLUSIONS

In summary, our study demonstrates that baseline serum chloride levels appear to have an independent and inverse association with the incidence of AF in patients with CKD. Lower serum chloride levels were also associated with an increased risk of incident HF, stroke, and all-cause death.

ACKNOWLEDGEMENTS

Thanks to Endi Cai and Aixin Guo, data researchers at the Digital Health China Technologies Co., Ltd, for their support and assistance.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethics committees of the participating centres approved the protocol of this study and waived patients' informed consent.

DISCLAIMER

The funders had no role in the study design, data collection analysis, decision to publish, or manuscript preparation.

FUNDING

This work was funded by the National Key R&D Program of China (No. 2021YFC2500200 and 2021YFC2500204), the Key Technologies R&D Program of Guangdong Province (No. 2023B1111030004), and the National Science Foundation of China (No. 82270743).

AUTHORS' CONTRIBUTIONS

Q.Y., F.H., Y.G., and S.N. conceptualized and designed the study. Q.Y. and Y.G. drafted the manuscript. Y.G. and S.N. contributed to the statistical analysis. M.P., R.H., H.L., Y.K., G.L., Q.W., Y. Zha, Y.H., G.X., Y.S., Y. Zhou, G.S., Y.T., and M.C.G. contributed to the data acquisition. All the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. Y.G. and S.N. contributed equally to this work.

DATA AVAILABILITY STATEMENT

Please contact Dr Q. Yang at yangqq@mail.sysu.edu.cn for access to the identified individual level-data.

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

REFERENCES

1. Webster AC, Nagler EV, Morton RL *et al*. Chronic kidney disease. *Lancet* 2017;**389**:1238–52. https://doi.org/10.1016/S0140-6736(16)32064-5
2. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. *Adv Exp Med Biol* 2019;**1165**:3–15. https://doi.org/10.1007/978-981-13-8871-2_1
3. Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;**395**:709–33. https://doi.org/10.1016/S0140-6736(20)30045-3
4. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR *et al*. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–52. https://doi.org/10.1016/S0140-6736(13)60595-4
5. Krahn AD, Manfreda J, Tate RB *et al*. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* 1995;**98**:476–84. https://doi.org/10.1016/S0002-9343(99)80348-9
6. Benjamin EJ, Muntner P, Alonso A *et al*. Heart Disease and Stroke statistics-2019 update: a report from the American Heart Association. *Circulation* 2019;**139**:e56–e528. https://doi.org/10.1161/CIR.0000000000000659
7. Hart RG, Eikelboom JW, Brimble KS *et al*. Stroke prevention in atrial fibrillation patients with chronic kidney disease. *Can J Cardiol* 2013;**29**:S71–8. https://doi.org/10.1016/j.cjca.2013.04.005
8. Soliman EZ, Prineas RJ, Go AS *et al*. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC.). *Am Heart J* 2010;**159**:1102–7. https://doi.org/10.1016/j.ahj.2010.03.027
9. Ananthapanyasut W, Napan S, Rudolph EH *et al*. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**:173–81. https://doi.org/10.2215/CJN.03170509
10. Guo Y, Gao J, Ye P *et al*. Comparison of atrial fibrillation in CKD and non-CKD populations: a cross-sectional analysis from the Kailuan study. *Int J Cardiol* 2019;**277**:125–9. https://doi.org/10.1016/j.ijcard.2018.11.098
11. Hecking M, Karaboyas A, Saran R *et al*. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2012;**59**:238–48. https://doi.org/10.1053/j.ajkd.2011.07.013
12. Kovesdy CP, Lott EH, Lu JL *et al*. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation* 2012;**125**:677–84. https://doi.org/10.1161/CIRCULATIONAHA.111.065391

13. Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance hemodialysis. *Am J Med* 2011;**124**:77–84. https://doi.org/10.1016/j.amjmed.2010.07.029
14. Kovesdy CP, Matsushita K, Sang Y *et al*. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. *Eur Heart J* 2018;**39**:1535–42. https://doi.org/10.1093/eurheartj/ehy100
15. Schrier RW, Sharma S, Shchekochikhin D. Hyponatraemia: more than just a marker of disease severity? *Nat Rev Nephrol* 2013;**9**:37–50. https://doi.org/10.1038/nrneph.2012.246
16. Rusinaru D, Tribouilloy C, Berry C *et al*. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis(dagger): meta-Analysis Global Group in chronic heart failure (MAGGIC). *Eur J Heart Fail* 2012;**14**:1139–46.
17. Goyal A, Spertus JA, Gosch K *et al*. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* 2012;**307**:157–64. https://doi.org/10.1001/jama.2011.1967
18. Grodin JL, Verbrugge FH, Ellis SG *et al*. Importance of abnormal chloride homeostasis in stable chronic heart failure. *Circ Heart Fail* 2016;**9**:e002453. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002453
19. Grodin JL, Testani JM, Pandey A *et al*. Perturbations in serum chloride homeostasis in heart failure with preserved ejection fraction: insights from TOPCAT. *Eur J Heart Fail* 2018;**20**:1436–43. https://doi.org/10.1002/ejhf.1229
20. Wu C, Zhang Y, Nie S *et al*. Predicting in-hospital outcomes of patients with acute kidney injury. *Nat Commun* 2023;**14**:3739. https://doi.org/10.1038/s41467-023-39474-6
21. Xu X, Nie S, Xu H *et al*. Detecting neonatal AKI by serum cystatin C. *J Am Soc Nephrol* 2023;**34**:1253–63. https://doi.org/10.1681/ASN.0000000000000125
22. Zhou S, Su L, Xu R *et al*. Statin initiation and risk of incident kidney disease in patients with diabetes. *CMAJ* 2023;**195**:E729–E38. https://doi.org/10.1503/cmaj.230093
23. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–266.
24. Von Elm, E, Altman DG *et al*. The strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;**370**:1453–7.
25. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
26. Go AS, Hylek EM, Phillips KA *et al*. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370–5. https://doi.org/10.1001/jama.285.18.2370
27. Bansal N, Fan D, Hsu CY *et al*. Incident atrial fibrillation and risk of death in adults with chronic kidney disease. *J Am Heart Assoc* 2014;**3**:e001303. https://doi.org/10.1161/JAHA.114.001303
28. Hindricks G, Potpara T, Dagres N *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
29. Govindarajulu US, Malloy EJ, Ganguli B *et al*. The comparison of alternative smoothing methods for fitting non-linear exposure-response relationships with Cox models in a simulation study. *Int J Biostat* 2009;**5**:Article 2. https://doi.org/10.2202/1557-4679.1104
30. Kotchen TA, Luke RG, Ott CE *et al*. Effect of chloride on renin and blood pressure responses to sodium chloride. *Ann Intern Med* 1983;**98**:817–22. https://doi.org/10.7326/0003-4819-98-5-817
31. Lorenz JN, Weihprecht H, Schnermann J *et al*. Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. *Am J Physiol* 1991;**260**:F486–93.
32. Schnermann J, Ploth DW, Hermle M. Activation of tubuloglomerular feedback by chloride transport. *Pflugers Arch* 1976;**362**:229–40. https://doi.org/10.1007/BF00581175
33. Kurtz TW, Morris RC, Jr. Dietary chloride as a determinant of "sodium-dependent" hypertension. *Science* 1983;**222**:1139–41. https://doi.org/10.1126/science.6648527
34. Kouyoumdzian NM, Kim G, Rudi MJ *et al*. Clues and new evidences in arterial hypertension: unmasking the role of the chloride anion. *Pflugers Arch* 2022;**474**:155–76. https://doi.org/10.1007/s00424-021-02649-5
35. Berend K, Van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? *Eur J Intern Med* 2012;**23**:203–11. https://doi.org/10.1016/j.ejim.2011.11.013
36. De Bacquer D, De Backer G, De Buyzere M *et al*. Is low serum chloride level a risk factor for cardiovascular mortality? *J Cardiovasc Risk* 1998;**5**:177–84.
37. Grodin JL, Simon J, Hachamovitch R *et al*. Prognostic role of serum chloride levels in acute decompensated heart failure. *J Am Coll Cardiol* 2015;**66**:659–66. https://doi.org/10.1016/j.jacc.2015.06.007
38. Ter Maaten JM, Damman K, Hanberg JS *et al*. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail* 2016;**9**.
39. Bei HZ, You SJ, Zheng D *et al*. Prognostic role of hypochloremia in acute ischemic stroke patients. *Acta Neurol Scand* 2017;**136**:672–9. https://doi.org/10.1111/ane.12785
40. McCallum L, Jeemon P, Hastie CE *et al*. Serum chloride is an independent predictor of mortality in hypertensive patients. *Hypertension* 2013;**62**:836–43. https://doi.org/10.1161/HYPERTENSIONAHA.113.01793
41. Zhang Z, Xu X, Fan H *et al*. Higher serum chloride concentrations are associated with acute kidney injury in unselected critically ill patients. *BMC Nephrol* 2013;**14**:235. https://doi.org/10.1186/1471-2369-14-235
42. Mandai S, Kanda E, Iimori S *et al*. Association of serum chloride level with mortality and cardiovascular events in chronic kidney disease: the CKD-ROUTE study. *Clin Exp Nephrol* 2017;**21**:104–11. https://doi.org/10.1007/s10157-016-1261-0
43. Khatri M, Zitovsky J, Lee D *et al*. The association between serum chloride levels and chronic kidney disease progression: a cohort study. *BMC Nephrol* 2020;**21**:165. https://doi.org/10.1186/s12882-020-01828-3
44. Wizemann V, Tong L, Satayathum S *et al*. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int* 2010;**77**:1098–106. https://doi.org/10.1038/ki.2009.477
45. Wetmore JB, Mahnken JD, Rigler SK *et al*. The prevalence of and factors associated with chronic atrial fibrillation

in Medicare/Medicaid-eligible dialysis patients. *Kidney Int* 2012;**81**:469–76. https://doi.org/10.1038/ki.2011.416
46. Genovesi S, Pogliani D, Faini A *et al*. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. *Am J Kidney Dis* 2005;**46**:897–902. https://doi.org/10.1053/j.ajkd.2005.07.044
47. Laukkanen JA, Zaccardi F, Karppi J *et al*. Reduced kidney function is a risk factor for atrial fibrillation. *Nephrology (Carlton)* 2016;**21**:717–20. https://doi.org/10.1111/nep.12727
48. Bansal N, Zelnick LR, Alonso A *et al*. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin J Am Soc Nephrol* 2017;**12**:1386–98. https://doi.org/10.2215/CJN.01860217
49. Eustace JA, Astor B, Muntner PM *et al*. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. *Kidney Int* 2004;**65**:1031–40. https://doi.org/10.1111/j.1523-1755.2004.00481.x
50. Krijthe BP, Heeringa J, Kors JA *et al*. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol* 2013;**168**:5411–5. https://doi.org/10.1016/j.ijcard.2013.08.048
51. Lopez FL, Agarwal SK, Grams ME *et al*. Relation of serum phosphorus levels to the incidence of atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] study.). *Am J Cardiol* 2013;**111**:857–62. https://doi.org/10.1016/j.amjcard.2012.11.045
52. Alonso A, Rooney MR, Chen LY *et al*. Circulating electrolytes and the prevalence of atrial fibrillation and supraventricular ectopy: the Atherosclerosis Risk in Communities (ARIC) study. *Nutr Metab Cardiovasc Dis* 2020;**30**:1121–9. https://doi.org/10.1016/j.numecd.2020.03.010
53. Piala AT, Moon TM, Akella R *et al*. Chloride sensing by WNK1 involves inhibition of autophosphorylation. *Sci Signal* 2014;**7**:ra41. https://doi.org/10.1126/scisignal.2005050
54. Bazua-Valenti S, Chavez-Canales M, Rojas-Vega L *et al*. The effect of WNK4 on the Na^+-Cl^- cotransporter is modulated by intracellular chloride. *J Am Soc Nephrol* 2015;**26**:1781–6. https://doi.org/10.1681/ASN.2014050470
55. Kahle KT, Rinehart J, Lifton RP. Phosphoregulation of the Na-K-2Cl and K-Cl cotransporters by the WNK kinases. *Biochim Biophys Acta* 2010;**1802**:1150–8. https://doi.org/10.1016/j.bbadis.2010.07.009
56. Yang CL, Zhu X, Ellison DH. The thiazide-sensitive Na-Cl cotransporter is regulated by a WNK kinase signaling complex. *J Clin Invest* 2007;**117**:3403–11. https://doi.org/10.1172/JCI32033
57. Adkins GB, Curtis MJ. Potential role of cardiac chloride channels and transporters as novel therapeutic targets. *Pharmacol Ther* 2015;**145**:67–75. https://doi.org/10.1016/j.pharmthera.2014.08.002
58. Clemo HF, Feher JJ, Baumgarten CM. Modulation of rabbit ventricular cell volume and $Na^+/K^+/2Cl^-$ cotransport by cGMP and atrial natriuretic factor. *J Gen Physiol* 1992;**100**:89–114. https://doi.org/10.1085/jgp.100.1.89
59. Orchard CH, Cingolani HE. Acidosis and arrhythmias in cardiac muscle. *Cardiovasc Res* 1994;**28**:1312–9. https://doi.org/10.1093/cvr/28.9.1312
60. Orchard CH, Kentish JC. Effects of changes of pH on the contractile function of cardiac muscle. *Am J Physiol* 1990;**258**:C967–81. https://doi.org/10.1152/ajpcell.1990.258.6.C967

Received: 5.11.2023; Editorial decision: 11.4.2024