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ORIGINAL RESEARCH

Prevalence and Mortality of Hypochloremia Among Patients with Coronary Artery Disease: A Cohort Study

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Purpose: Hypochloremia is a predictor for short-term mortality in patients with cardiovascular disease, but its association with coronary artery disease (CAD) is still unclear. We aimed to assess the impact of hypochloremia on all-cause mortality (short-and long-term) among patients with CAD.

Patients and Methods: Based on the registry at Guangdong Provincial People's Hospital in China, we analyzed data of 49,025 hospitalized patients who underwent coronary angiography (CAG) and were diagnosed with CAD from January 2007 to December 2018. To assess the association between hypochloremia and the study endpoints, a logistic-regression model (for 30-day all-cause mortality) and a Cox regression model (for long-term all-cause mortality) were fitted.

Results: Overall, 4.4% of the study population showed hypochloremia (<98 mmol/L). During a median follow-up of 5.2 (3.1–7.8) years, a total of 6486 (13.2%) patients died. Patients with hypochloremia were generally older and at risk for diabetes, cardiorenal dysfunction, and morbidity than those without hypochloremia. After adjustment for confounders, hypochloremia remained a significant predictor of mortality risk (30-day all-cause death: adjusted odds ratio [aOR], 1.99; 95% confidence interval, 1.08–3.18; P=0.017 and long-term all-cause death: adjusted hazard ratio [aHR], 1.32; 95% confidence interval, 1.19–1.47; P<0.001).

Conclusion: Hypochloremia is mildly common in patients with CAD and is associated with increased short-and long-term mortality. Meanwhile, it is necessary to further investigate effective and preventive measures and the potential mechanisms of hypochloremia in patients with CAD.

Keywords: hypochloremia, coronary artery disease, prevalence, short- and long-term mortality

Introduction

Several clinical studies have shown hypochloremia is an independent predictor for short-term mortality among patients with cardiovascular disease (CVD) such as acute or chronic heart failure[1–4] and hypertension.[5] The association of hypochloremia with short-term mortality is more pronounced in patients with chronic kidney disease (CKD) and postoperative patients with coronary artery disease (CAD) confirmed by coronary angiography (CAG).[6–8] The correlation between hypochloremia and long-term mortality is poorly understood, but potential mechanisms are linked to the loss of gastrointestinal tract, fluid-related imbalance of adrenal hormones, and inflammatory response.[9,10]

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CAD forms a major proportion of all CVDs and is the leading cause of global morbidity and mortality, which is often accompanied with heart failure, hypertension, and CKD.[11,12] Given the significant role of hypochloremia in patients with CVD, we hypothesized that it may be also an important prognostic factor of short- and long-term mortality in patients with CAD. Therefore, we aimed to assess the prevalence and mortality (short- and long-term) of hypochloremia among CAD patients.

Patients and Methods

Data Collection

From January 2007 to December 2018, data were extracted from the electronic clinical management records system of the Guangdong Provincial People's Hospital (ClinicalTrials.gov NCT04407936). The baseline information included patient demographics, laboratory test results, mortality, and other clinical variables. Patients' blood samples were collected early morning after they were fasted overnight for measurement of baseline chloride ion concentration. Drugs and other treatments at admission are judged by experienced clinicians. Data on follow-up information was mainly performed by telephone or clinical visit and partly missing dates will be obtained from the Guangdong Provincial Public Security which was matched to the electronic Clinical Management System of the Guangdong Provincial People's Hospital records according to the unique ID number of patients.

Study Population

This was a single-center, observational, retrospective cohort study that included patients with CAG-confirmed CAD according to the 10th Revision Codes of the International Classification of Diseases (ICD-10; I20.xx–I25.xx, I50.00001, and I91.40001, Supplemental Table S1) at the Guangdong Provincial People's Hospital, Guangdong, China, from January 2007 to December 2018. Coronary angiography or percutaneous coronary intervention (PCI) was performed following standard clinical practice guidelines.[13,14] We excluded patients with missing data on follow-up evaluation and serum chloride levels and those with cancer. Eventually, 49,025 patients were included for the final analysis (Figure 1).

The study protocol was approved by the GDPH ethics committee (No. GDREC2019555H [R1]), and the study was performed according to the tenets of the Helsinki declaration. All identifiable personal information were removed from the analytic dataset to protect patients' privacy. The ethics committee of Guangdong Provincial People's Hospital waived the need for informed consent for this study because it was a a retrospective study. We hided all the personal information of patients, and the study would not cause any damage to patients.

Endpoints and Definition

The primary endpoint of this study was the 30-day postadmission all-cause death and long-term all-cause death. Hypochloremia was defined according to the baseline

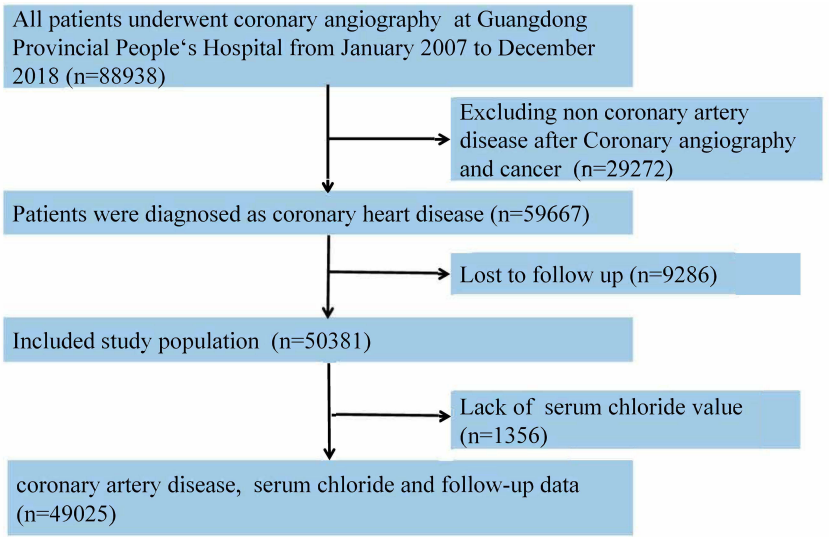

Figure 1 The flow of participants through the trial.

chloride concentration (<98 mmol/L) of venous blood drawn at admission. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.[15] Acute myocardial infarction (AMI), diabetes mellitus (DM), and hypertension were defined by the 10th Revision Codes of the International Classification of Diseases (Supplemental Table 1).

Statistical Analysis

Descriptive statistics are reported as the mean (standard deviation [SD]), or number and percentage when appropriate. Differences between groups were analyzed using the Student's *t*-test. Pearson chi-squared tests were used to analyze categorical data.

Time-to-event data were presented graphically using Kaplan–Meier curves (Figure 3 and Supplemental Figure 1). Log rank tests were used to compare survival between groups. Restricted cubic splines were used to investigate the associations of serum chlorine levels with long-term all-cause death and the 30-day all-cause death after adjusting for age and sex (Figure 2). To assess the association between hypochloremia and the study endpoints, a logistic regression model (for 30-day all-cause mortality) and a Cox regression model (for long-term all-cause mortality and 30-day all-cause mortality) was fitted (Table 2 and Supplemental Table 2). Model 1 was unadjusted; model 2 was to adjusted for age (as a continuous variable) and sex; and model 3 included the variables that were associated with mortality according to clinical experience (it included the variables from Models 1 and 2, history of present illness information, and drugs information). Finally, we defined the results of Model 3 as the primary results. We also performed a subgroup analysis among six prespecified subgroups (sex, acute coronary syndromes [ACS], DM, CKD, use of diuretics, and older [age>65 years]) to assess the impact of hypochloremia on long-term all-cause mortality among CAD patients. All P-values were two-sided, and P<0.05 was considered to indicate statistical significance. All statistical analyses were performed using R (ver. 4.0.3).

Results

The Characteristics of Patients

According to the cut-off value of the serum chloride level (98 mmol/L), 49,025 patients with CAD were divided into two groups (hypochloremia [<98 mmol/L] vs non-hypochloremia [≥98 mmol/L]). The percentage of patients with hypochloremia was 4.4% (n=2162). The mean age of the cohort was 63.0±10.7 years; 24% patients were male; 9773 had AMI (20.0%); 3074 had pre-MI (6.3%); and 35,755 (73%) underwent PCI.

Serum chloride was normally distributed, and the mean serum chloride level in the hypochloremia and non-hypochloremia groups was 105.0±3.1 mmol/L and 95.1 ±2.9 mmol/L, respectively. Patients with CAD who had hypochloremia tended to be older and of female sex. Patients with hypochloremia were positively associated with CHF (1.0% vs 0.5%, P=0.006); DM (42.7% vs 26.9%, P<0.001); hypertension (62.6% vs 56.2%, P<0.001); anemia (39.8% vs 31.8%, P<0.001); CKD (37.9% vs 21.4%, P<0.001); and ACS (52.3% vs 44.2%, P<0.001). Some biochemical markers such as high-density

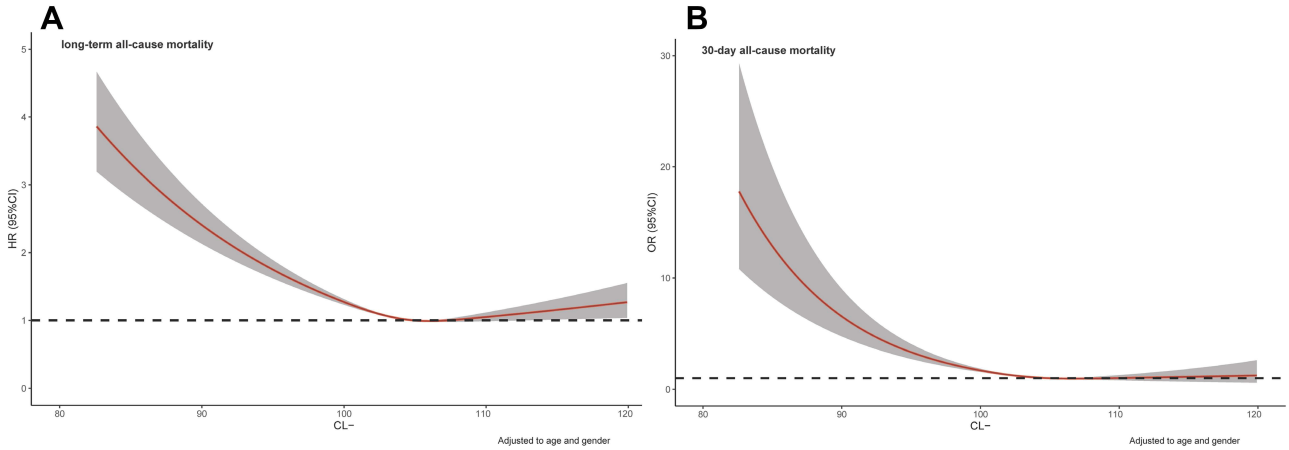

Figure 2 Restricted spline curve for the chloride ion hazard ratio. (**A**) long-term mortality; (**B**) 30-day mortality; adjusted for age and sex.

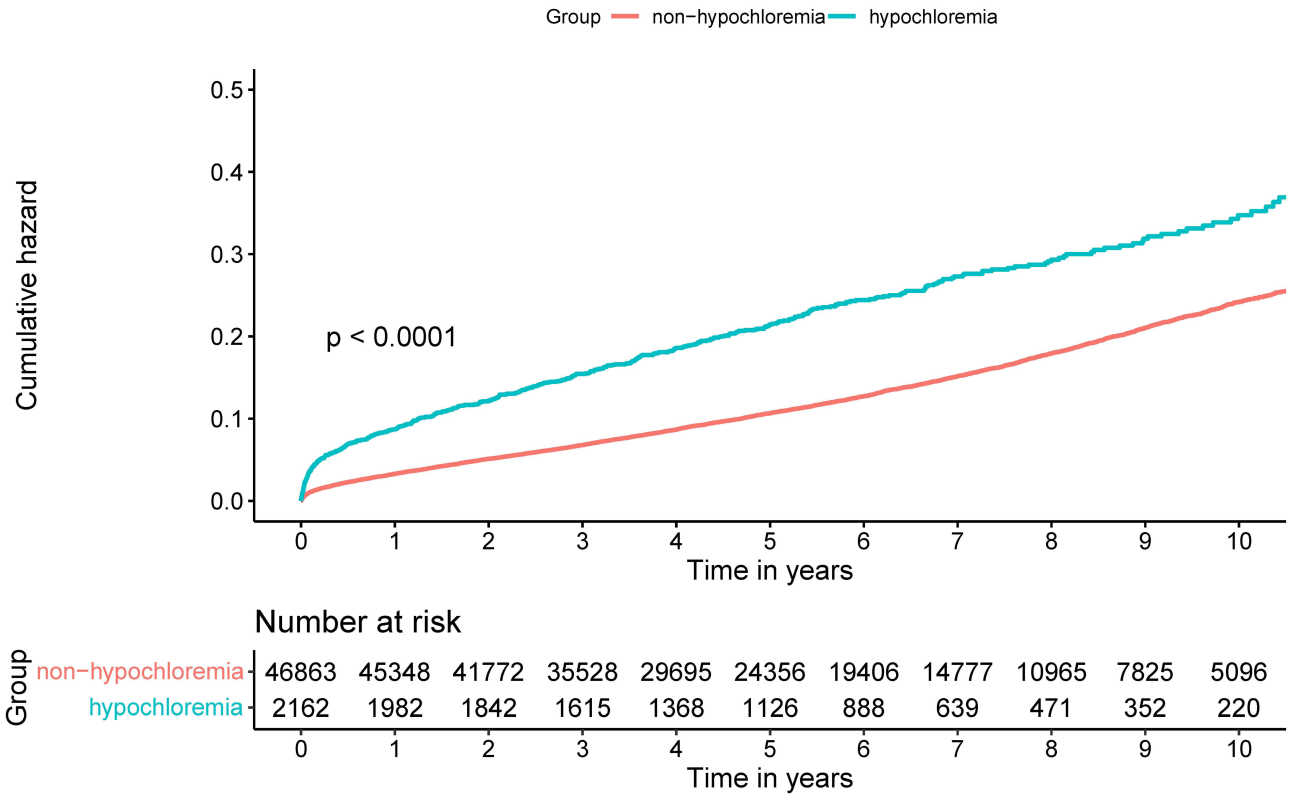

Figure 3 Kaplan–Meier curves for long-term all-cause mortality of hypochloremia.

lipoprotein cholesterol, sodium ions, albumin, hepatic enzymes, and routine blood index were associated with hypochloremia. In addition, patients with hypochloremia often used more diuretics, either loop diuretics or mineralocorticoid receptor antagonists. More details of the baseline characteristics of patients enrolled are shown in Table 1.

Chloride Levels and Clinical Endpoints

During a median follow-up of 5.2 (3.1–7.8) years, a total of 6486 (13.2%) patients died. In the 30-day follow-up after admission, 538 patients (1.1%) died of all causes. In hypochloremia patients, an inverse association was observed between the hazard ratio (HR)/odds ratio (OR) for the endpoints and chloride level (Figure 2). Kaplan–Meier analysis showed that hypochloremia would have a higher long-term all-cause mortality than non-hypochloremia. (Figure 3, log-rank, p<0.0001) The relationships between all-cause mortality and hypochloremia were evaluated using Cox proportional hazards models, which showed that hypochloremia was associated with a higher risk of 30-day all-cause death even after full adjustment of major confounders (OR: 1.99, 95% CI: 1.08–3.38, P<0.01) than normal serum chloride level (Table 2). Importantly, it suggested that admission chloride level was an independent predictor of long-term all-cause death. Hypochloremia was associated with a higher risk of long-term all-cause death (model 1: HR 1.79, 95% CI 1.64–1.97, P<0.001; model 2: HR 1.65, 95% CI 1.50–1.81, P<0.001; and model 3: HR 1.32, 95% CI 1.19–1.47, P=0.017) than normal serum chloride level (Table 2).

In the subgroup analysis, Cox regression analysis revealed that hypochloremia had a relatively consistent risk of mortality across dichotomized subgroups (DM, CKD, age>65 years, sex, ACS, and use of diuretics) (Table 3).

Discussion

To our knowledge, this is the first study to explore the prevalence of and mortality associated with hypochloremia among CAD patients. Our study indicated that 4.4% CAD patients had hypochloremia, and an inverse association was found between admission chloride levels and short- and long-term mortality among patients with CAD. Further, similar results were observed among the different subgroups.

Table 1 Baseline Characteristics of the Patients

Characteristic	Overall (n=49,025)	Non-Hypochloremia (n=46,863)	Hypochloremia (n=2162)	P value
Demographic characteristics				
Female, n (%)	11,777 (24.0)	11,170 (23.8)	607 (28.1)	<0.001
Age, years, mean (SD)	63.01 (10.7)	62.87 (10.7)	66.00 (10.7)	<0.001
Medical history				
Anemia, n (%)	15,558 (32.1)	14,706 (31.8)	852 (39.8)	<0.001
ACS, n (%)	21,797 (44.5)	20,668 (44.2)	1129 (52.3)	<0.001
AMI, n (%)	9773 (20.0)	9096 (19.4)	677 (31.4)	<0.001
CHF, n (%)	260 (0.5)	239 (0.5)	21 (1.0)	0.006
DM, n (%)	13,515 (27.6)	12,594 (26.9)	921 (42.7)	<0.001
CKD, n (%)	8875 (22.2)	8139 (21.4)	736 (37.9)	<0.001
Prior AMI, n (%)	3074 (6.3)	2922 (6.2)	152 (7.0)	0.147
PCI, n (%)	35,755 (72.9)	34,133 (72.8)	1622 (75.0)	0.027
Hypertension, n (%)	27,647 (56.5)	26,295 (56.2)	1352 (62.6)	<0.001
Laboratory tests				
CHOL, mmol/L, mean (SD)	4.5 (1.2)	4.54 (1.2)	4.6 (1.4)	0.008
TRIG, mmol/L, mean (SD)	1.7 (1.2)	1.7 (1.2)	1.8 (1.8)	<0.001
LDLC, mmol/L, mean (SD)	2.8 (1.0)	2.8 (1.0)	2.8 (1.0)	0.712
HDLC, mmol/L, mean (SD)	1.00 (0.26)	1.00 (0.26)	1.02 (0.32)	<0.001
LYMPH,10^9/L, (mean (SD))	1.9 (0.7)	1.9 (0.7)	1.7 (0.7)	<0.001
WBC,10^9/L (mean (SD))	8.0 (2.8)	8.0 (2.7)	9.5 (3.7)	<0.001
NEUT,10^9/L (mean (SD))	5.2 (2.6)	5.2 (2.6)	6.9 (3.6)	<0.001
PLT,10^9/L (mean (SD))	226.5 (69.4)	225.7 (68.5)	243.8 (84.9)	<0.001
LVEF, % (mean (SD))	58.9 (12.1)	59.1 (11.9)	53.2 (14.2)	<0.001
lg (proBNP), mean (SD)	2.5 (0.8)	2.4 (0.8)	3.0 (0.9)	<0.001
eGFR, mL/min/1.73m2 (mean (SD))	77.5 (25.4)	77.9 (24.9)	69.2 (31.6)	<0.001
K, mmol/L, mean (SD)	3.8 (0.4)	3.8 (0.4)	3.8 (0.6)	0.541
Ca, mmol/L, mean (SD)	2.2 (0.1)	2.2 (0.1)	2.2 (0.2)	0.247
Na, mmol/L, mean (SD)	139.0 (3.00)	139.3 (2.6)	133.5 (4.8)	<0.001
CL, mmol/L, mean (SD)	104.6 (3.7)	105.0 (3.6)	95.1 (2.9)	<0.001
HbA1c, % (mean (SD))	6.6 (1.4)	6.5 (1.4)	7.3 (1.9)	<0.001
hs-CRP, mg/dL (mean (SD))	11.9 (25.4)	11.0 (23.3)	31.0 (50.7)	<0.001
AST, U/L (mean (SD))	51.8 (199.5)	50.4 (186.5)	82.5 (386.2)	<0.001
ALT, U/L (mean (SD))	34.9 (88.7)	34.2 (80.4)	50.9 (195.6)	<0.001
ALB, g/L (mean (SD))	36.3 (4.2)	36.40 (4.2)	34.7 (5.1)	<0.001

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (n=49,025)	Non-Hypochloremia (n=46,863)	Hypochloremia (n=2162)	P value
Medications				
ACEI/ARB, n (%)	23,905 (49.7)	22,926 (49.8)	979 (47.6)	0.056
Beta-blockers, n (%)	38,995 (81.1)	37,342 (81.1)	1653 (80.4)	0.438
CCB, n (%)	10,063 (20.9)	9624 (20.9)	439 (21.4)	0.645
Statin, n (%)	45,574 (94.8)	43,669 (94.9)	1905 (92.7)	<0.001
Antiplatelet, n (%)	46,082 (95.8)	44,137 (95.9)	1945 (94.6)	0.006
Loop diuretics, n (%)	6632 (13.8)	6051 (13.1)	581 (28.3)	<0.001
MRA, n (%)	6891 (14.3)	6292 (13.7)	599 (29.1)	<0.001
Diuretics	9104 (18.4)	8376 (18.2)	728 (35.4)	<0.001

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ALB, albumin; ALT, alanine transaminase; AMI, acute myocardial infarction; AST, Aspartate aminotransferase; CCB, calcium channel blocker; CHF, congestive heart failure; CHO, serum total cholesterol; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LYMPN, lymphocyte; NEUT, neutrophil; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; PLT, blood platelet; Prior AMI, prior acute myocardial infarction; proBNP, pro-brain Natriuretic Peptide; TG, triglycerides; WBC, white blood cell;.

Chloride is the most abundant anion in the extracellular fluid.[10] Some studies have reported that the regulation of macula densa renin secretion in the kidneys may be dependent on chloride.[16] Chloride plays an important role in the acid-base balance, muscle activity, and immune regulation.[17] The adverse outcomes of hyponatremia have been elucidated in previous studies.[18–23] Despite being a counter anion of sodium, chloride has not gained as much attention as sodium, but in recent years, chloride ion studies have gained more focus.[1,2,5,6,24–28] An earlier study has shown that hypochloremia observed within 48 h after surgery was not rare and was independently associated with the increased risk of in-hospital mortality.[7] However, the evidence of prognostic value for patients with CAD is not sufficient. Our study reveals that chloride could be a prognostic factor for patients with CAD, which is consistent with some previous studies.

The exact mechanisms underlying the link between hypochloremia and CAD are unknown; hence, several hypotheses have been proposed. First, a likely reason for the relation of hypochloremia to short- and long-term mortality is that low chloride levels might upregulate inflammatory cytokines that could promote the inflammation process[29] and are well-known predictors of poor outcome and mortality in CAD.[30–32] Second, chloride ions have a critical role in regulatory pathways central to physiological stability. For example, low chloride reflects a high anion gap and high renin levels,[5,33,34] associated with high blood pressure.[35] Additionally, several chloride ion channels with important regulatory functions have been identified or further characterized recently.[20,31] Third, according to our results, hypochloremia could be considered a marker of clinical complexity, because it is observed more often in older patients with DM, CKD, hypertension, and anemia than others, which eventually leads to a significantly increased mortality risk.[32–36]

Given the growing body of literature demonstrating the risk of hypochloremia, we conducted research relevant to the relation between hypochloremia and CAD mortality. We evaluated the impact of outcomes among CAD patients. It is possible that hypochloremia is a therapeutic target that could be amenable to treatment with acetazolamide or chloride supplementation. Our study suggests that hypochloremia is a therapeutic target that is amenable to treatment with chloride supplementation in CAD patients. Moreover, it is also important to prospectively evaluate the mechanism of hypochloremia on the outcome (short- and long-term mortality) in all CAD patients.

Limitations

Our study has some limitations. First, this was a single-center retrospective cohort study with selection bias. For

Table 2 The Association Between Hypochloremia and the Study Endpoints in Different Models

A. Logistic proportional odds ratios for 30-day all-cause mortality in different models					
			30-day all-cause mortality		
	n	Events, n (%)	OR/HR, 95%CI, p-value		
			Model 1*	Model 2[$]	Model 3[§]
Non-hypochloremia	46,863	464 (1%)	ref	ref	ref
Hypochloremia	2162	74 (3.4%)	3.54 (2.74–4.52), <0.001	3.09 (2.39–3.94), <0.001	1.99 (1.08–3.38), 0.03
B.Cox proportional hazard ratios for long-term all-cause mortality in different models					
Non-hypochloremia	46,863	6007 (12.8%)	ref	ref	ref
Hypochloremia	2162	479 (22.2%)	1.79 (1.64–1.97), <0.001	1.65 (1.50–1.81), <0.001	1.32 (1.19–1.47), <0.001

Notes: *Unadjusted; [$]Adjusted for age and gender; [§]Adjusted for full multivariate: age, gender, hypertension, acute myocardial infarction, pre-acute myocardial infarction, diabetes mellitus, percutaneous coronary intervention, anemia, chronic kidney disease, congestive heart failure, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, β-blockers, calcium channel blockers, antiplatelet agent.

Table 3 Hazard Ratios for the Long-Term All-Cause Mortality in Different Subgroups (Hypochloremia Vs Non- Hypochloremia)

	n	Long-Term All-Cause Mortality			
		HR	95%CI	P-value	P-interaction
DM	13,515	1.29	1.10–1.53	0.002	0.94
Non-DM	35,451	1.33	1.15–1.54	0.001	
CKD	8875	1.33	1.14–1.55	<0.001	0.45
Non-CKD	31,141	1.31	1.12–1.52	<0.001	
Male	37,014	1.32	1.17–1.50	<0.001	0.95
Female	11,686	1.32	1.06–1.63	0.01	
Diuretics	9104	1.18	1.01–1.39	0.04	0.49
Non-diuretics	38,991	1.37	1.13–1.52	<0.001	
ACS	21,797	1.32	1.14–1.54	<0.001	0.77
CCS	27,169	1.31	1.12–1.53	<0.001	
Older	20,712	1.29	1.13–1.48	<0.001	0.78
Non-older	28,313	1.34	1.12–1.60	0.001	

example, patients with more severe CAD may have been recruited into this study than other studies, because our patients were enrolled from the largest cardiovascular center in southern China. However, sizeable data extracted from medical records is allowed to control a variety of confounders in analyses. Second, information about cause-specific death including cardiovascular mortality was not available, and it is difficult to examine the significant correlation between hypochloremia and cause-specific death. Further studies are needed to explore the relationship between hypochloremia and cardiovascular death among CAD patients. Third, data of chloride levels were only extracted at admission without assessment of changes after discharge. Although the status of chloride and the effect of its changes were still unknown after discharge, the follow-up patient information about chloride is being collected for future analysis. In addition, although we have information on the use of diuretics, the information on dose is lacking. Therefore, this could not be analyzed further. Fourth, certain unknown and unmeasured risk factors remained in the analyses after adjusting various confounders to control bias. Last, blood gas analysis is the fundamental approach to study electrolyte disorders. As the diagnosis of hypochloremia in our study was based on venous blood, we ignored arterial chloride levels. Although we included all patients with coronary heart disease, not all data on arterial blood gas. In subsequent studies, it may be possible to analyze the

prognostic differences of chloride levels in arterial and venous blood.

Conclusion

Hypochloremia assessment could allow clinicians to identify patients with CAD at elevated risk for short- and long-term mortality. Adequate assessment of hypochloremia status and necessary chloride supplementation may help to improve the prognosis of patients with CAD. This information can have a substantial clinical impact on CAD patients with hypochloremia by prevention and active intervention in the early stage.

Data Sharing Statement

No additional data are available.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Role of the Funders/Sponsors

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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Disclosure

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