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RESEARCH ARTICLE

Association between serum chloride and in-hospital mortality in congestive heart failure with diabetes: Data from the MIMIC-IV database

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Abstract

Background Congestive heart failure (CHF) demonstrates a heightened prevalence in individuals with diabetes mellitus within Intensive Care Units. The occurrence of abnormal chloride levels is frequently observed in critically ill patients, yet its clinical significance remains subject to debate. This study endeavors to explore the relationship between serum chloride levels and in-hospital mortality among patients affected by both congestive heart failure and diabetes.

Methods A retrospective cohort study was conducted, utilizing data from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database, focusing on adult patients in the United States. The impact of serum chloride levels upon ICU admission on in-hospital mortality was analyzed using multivariable logistic regression models, generalized additive models and subgroup analysis.

Results The study encompassed 7,063 patients with coexisting diabetes and congestive heart failure. The fully adjusted model revealed an inverse association between serum chloride levels and in-hospital mortality. As a tertile variable (Q3 vs Q1), the odds ratio (OR) was 0.73 with a 95% confidence interval (CI) of 0.54–0.98 ($p = 0.039$). As a continuous variable, per 1 mmol/L increment, the OR (95% CI) was 0.97 (0.96–0.99, $p = 0.01$). The relationship between serum chloride and in-hospital mortality demonstrated linearity (non-linear $p = 0.958$). Stratified analyses further validated the robustness of this correlation.

Conclusions Serum chloride levels exhibited a negative association with in-hospital mortality in patients with both congestive heart failure and diabetes. Nevertheless, prospective, randomized, controlled studies are warranted to corroborate and validate the findings presented in this investigation.

Keywords Blood chloride · Congestive heart failure · Diabetes · Generalized additive model · In-hospital mortality

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Introduction

Diabetes mellitus is a prevalent chronic condition characterized by elevated blood glucose levels and disturbances in metabolism, including altered insulin secretion [1]. The International Diabetes Federation projects a significant increase in diabetes cases, with an estimated 643 million cases by 2030 and 783 million by 2045 [2]. Congestive heart failure is a widespread clinical syndrome that is on the rise in the United States [3]. It affects tens of millions of patients globally and continues to be a leading cause of hospitalization and mortality [4]. Epidemiological research has established a significant association between heart failure and diabetes mellitus (DM) [5–7]. Specifically, Type 2 diabetes (T2D) constitutes a risk factor for cardiovascular events, such as congestive heart failure (CHF), thereby heightening morbidity and mortality risks in patients [8]. Congestive heart failure ranks as the most prevalent cardiovascular complication of diabetes, surpassing the incidence of myocardial infarction or stroke [9]. Both diabetes and congestive heart failure share a common pathophysiological mechanism, underscoring the importance of managing their synergistic effects [8, 9]. Despite the growing recognition of the regulatory role of electrolytes in cardiovascular health and diabetes, their intricate interplay remains partially understood [10].

Chloride, as the second most abundant serum electrolyte following sodium [11], plays a pivotal role in the regulation of body fluids, electrolyte balance, and acid–base status. Moreover, it is indispensable for assessing various pathological conditions [12]. In recent decades, clinical practice has increasingly focused on serum chloride due to its crucial role in maintaining acid–base equilibrium and plasma electroneutrality [12–14]. Alterations in chloride levels have been observed in medical conditions such as fluid overload, congestive heart failure, renal, endocrine, and metabolic disorders [13]. Independent and inverse associations have been documented between serum chloride levels at admission and mortality in Acute Decompensated Heart Failure [15], as well as a strong and independent correlation between serum chloride levels and reduced survival in patients with chronic heart failure [16]. A separate study revealed that hyperchloremia in diabetic patients was linked to an extended time to diabetes resolution, an increased risk of in-hospital Acute Kidney Injury (AKI), and a longer hospital stay [17].

Despite the close connection between diabetes and heart failure, limited research has investigated the relationship between serum chloride levels among individuals with diabetes mellitus at the time of hospitalization for congestive heart failure and their outcomes. Consequently, this study seeks to explore the association between serum chloride levels and in-hospital mortality within a substantial cohort of American adults with congestive heart failure and diabetes admitted to the intensive care unit.

Method

Data source

This study employed data from the publicly accessible Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which comprises comprehensive clinical information from patients treated at Beth Israel Deaconess Hospital in Boston, Massachusetts, USA [18, 19]. MIMIC-IV is the outcome of a collaborative initiative between Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology [20]. The database encompasses a wide array of clinical data, including medical records, drug treatments, laboratory findings, patient characteristics, and International Classification of Diseases (ICD) codes [21]. Access to the MIMIC-IV database was granted to the first author, Kai Zhang, following successful completion of the 'Protecting Human Research Participants' examination (ID: 11639604) offered by the National Institutes of Health (NIH). Ethical approval for the database was obtained from the Institutional Review Board of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center [22]. To safeguard patient confidentiality, all personal information within the database was anonymized [10]. As a result, the requirement for informed consent and an ethical approval statement was waived for this study, which adhered to the principles of the Declaration of Helsinki [23]. Reporting of this cross-sectional study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [24].

Study population

The study included eligible participants who were admitted to the intensive care unit (ICU) with congestive heart failure (CHF) and coexisting diabetes. Ischemic CHF diagnosis was confirmed using the International Classification of Diseases, Ninth Revision (ICD-9) code 4280 [25]. Data from the initial ICU admission were included, even for patients with multiple admissions. Exclusion criteria applied to individuals under 18 years old, those with incomplete outcome data, and individuals without diabetes. Both the derivation and validation cohorts consisted of 7,063 CHF patients, as depicted in Fig. 1.

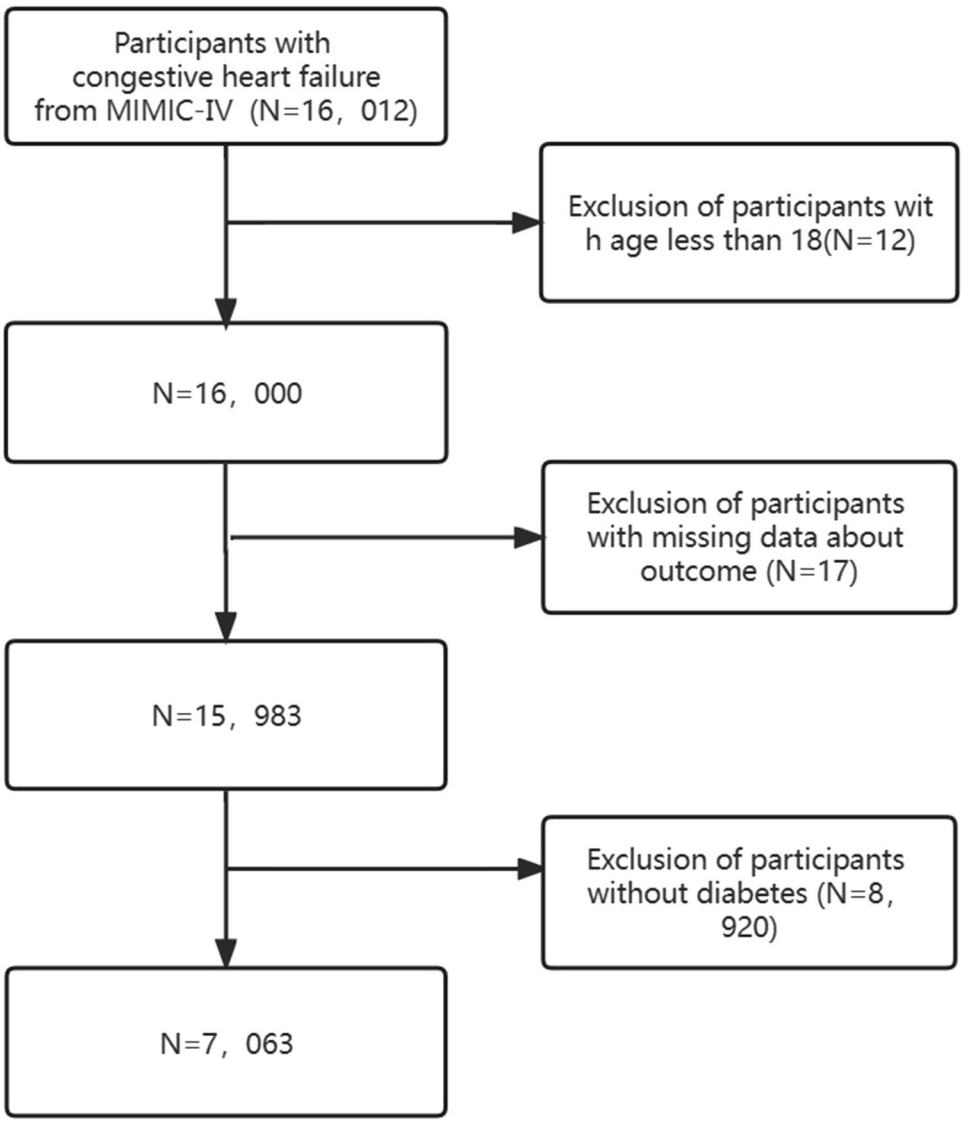

Fig. 1 Flowchart of patient selection

Data retrieval and outcomes

The Structured Query Language (SQL) was utilized for data extraction [26]. Within the initial 24 h of ICU admission, we collected comprehensive data, including vital signs, Sequential Organ Failure Assessment (SOFA) scores, Simplified Acute Physiology Score II (SAPS II), demographic information (age, race, sex), and indicators of illness severity at ICU entry using SOFA and SAPS II scores. Additionally, we documented treatment specifics such as the use of ventilation, vasoactive medications (norepinephrine, dopamine, epinephrine, phenylephrine, and vasopressin), and medical procedures such as intubation. Notably, we also recorded comorbidities such as chronic obstructive pulmonary disease (COPD), hepatic failure (Hep F), and acute myocardial infarction (AMI).

Upon admission, laboratory test indices included anion gap (AG), chloride, blood urea nitrogen (BUN), calcium, creatinine, potassium, sodium, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, hemoglobin, red blood cell distribution width (RDW), red blood cell count (RBC), and white cell count (WCC). Demographic characteristics and vital signs within the first 24 h of admission were captured, with the initial measurements at admission serving as laboratory examination indicators. Our goal was to extract identical variables as those found in the MIMIC-IV dataset. The primary outcome assessed was in-hospital mortality, determined by the patient's survival status at discharge.

Statistical analyses

Firstly, the data were initially categorized into continuous and categorical variables. Continuous variables were summarized as mean ± standard deviation and compared using Student's t-test if normally distributed, or as median ± interquartile range (IQR) and compared using the Wilcoxon rank-sum test if not normally distributed. Categorical variables were expressed as percentages and compared using the chi-square test. For continuous variables, differences among groups stratified by serum chloride levels were assessed using either the Kruskal–Wallis test or one-way analysis of variance (ANOVA).

In addition, multivariate logistic regression was conducted to investigate the association between serum chloride and in-hospital mortality. Various models were employed for adjustment, progressively incorporating covariates: Model 1: Crude model without any adjusted covariates. Model 2: Demographic variables (sex, age, race) were included. Model 3: Demographic variables and concomitant diseases (COPD, AMI, MC, HepF) were added. Model 4: Demographic variables, complicating diseases, medical procedures (Vent, Intubated), medication situation (Norepinephrine, Dopamine, Epinephrine, Phenylephrine, Vasopressin), basic vital signs (Temperature, Respiratory Rate, Heart Rate, SBP), and blood biochemical indicators (AG, BUN, Chloride, Creatinine, Hb, MCH, MCHC, MCV, Platelet, Potassium, Sodium, RBC, RDW, WBC) were further included. Model 5: Adjustment for demographic variables, complicating diseases, medical procedures, medication situation, basic vital signs, blood biochemical indicators, APSIII, SOFA. Tests for trend involved logistic regression with serum chloride categorized into three groups.

Finally, non-linear relationships between serum chloride and in-hospital mortality were examined using a Generalized Additive Model and a smooth curve fitting technique (penalized spline method). Stratified linear regression models and likelihood ratio tests were employed to identify modifications and interactions in subgroups based on various factors.

All statistical analyses were conducted using R, version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), and Free Statistics software, version 1.7 [27]. A significance level of $P < 0.05$ (two-sided) was considered statistically significant. The reporting of this cross-sectional study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Results

Baseline characteristics of selected participants

Table 1 outlines the baseline characteristics of 7063 patients diagnosed with both diabetes and congestive heart failure (CHF). These patients were stratified into three tertiles based on their serum chloride levels: Q1 (≤ 98 mmol/L), Q2 (98–104 mmol/L), and Q3 (> 104 mmol/L). The mean age for the entire patient cohort was 71.5 ± 12.2 years.

Patients with elevated serum chloride levels exhibited several distinct characteristics compared to those with lower levels. Specifically, they tended to be older, had a higher proportion of Caucasian individuals, an increased utilization of ventilators and intubation, a reduced incidence of chronic obstructive pulmonary disease (COPD), higher body temperature, and lower values for respiratory rate, heart rate, anion gap (AG), blood urea nitrogen (BUN), creatinine levels, mean corpuscular hemoglobin concentration (MCHC), and blood potassium levels. Moreover, they displayed higher blood sodium levels and decreased platelet count, red blood cell (RBC) count, and red cell distribution width (RDW). Additionally, the mortality rate was lower in this particular patient group.

Association between serum chloride and In-hospital mortality

Table 2 displays the correlation between serum chloride levels and in-hospital mortality in patients afflicted with both congestive heart failure and diabetes. To explore the independent influence of serum chloride on in-hospital mortality, five primary models were constructed employing multivariate binary logistic regressions. The resulting effect sizes (OR), accompanied by their respective 95% confidence intervals (CI) and *P* values, are presented in Table 2.

When treating serum chloride as a continuous variable, each one-unit increase (1 mmol/L) corresponded to a 2% decrease in the risk of in-hospital mortality (OR: 0.98; 95% CI: 0.97–0.99). This association remained statistically significant even after adjusting for covariates in models 2 to 4. In model 5, which accounted for all covariates, each one-unit increase in serum chloride was linked to a 3% reduction in the risk of in-hospital mortality (OR: 0.97; 95% CI: 0.96–0.99).

Additionally, when serum chloride was investigated as a categorical variable within the fully adjusted model (model 5), a discernible trend emerged. Relative to the lowest serum chloride category (Q1), the adjusted odds ratios (ORs) for Q2 and Q3 were 0.89 (95% CI: 0.7–1.13) and 0.73 (95% CI: 0.54–0.98), respectively. The trend analysis yielded a statistically significant result ($p = 0.039$).

Dose–Response Relationships

The study employed a logistic regression model with a cubic spline function to examine the relationship between Blood Chloride levels and In-hospital mortality. Figure 2 illustrates variable distributions (blue histograms), the smoothing

Table 1 Characteristics of the study population ($N=7063$)

Variables	Total ($n=7063$)	Q1 ($n=2176$)	Q2 ($n=2523$)	Q3 ($n=2364$)	P value [a]
Age, Mean ± SD	71.5 ± 12.2	69.4 ± 12.3	72.1 ± 12.3	72.9 ± 11.8	< 0.001
Gender, n (%)					0.841
Male	3928 (55.6)	1210 (55.6)	1393 (55.2)	1325 (56)	
Female	3135 (44.4)	966 (44.4)	1130 (44.8)	1039 (44)	
Race, n (%)					0.028
White	4449 (63.0)	1320 (60.7)	1610 (63.8)	1519 (64.3)	
Black	1275 (18.1)	430 (19.8)	455 (18)	390 (16.5)	
Other	1339 (19.0)	426 (19.6)	458 (18.2)	455 (19.2)	
Medication situation					
Norepinephrine, n (%)					< 0.001
No	5349 (75.7)	1615 (74.2)	1976 (78.3)	1758 (74.4)	
Yes	1714 (24.3)	561 (25.8)	547 (21.7)	606 (25.6)	
Dopamine, n (%)					< 0.001
No	6831 (96.7)	2077 (95.5)	2459 (97.5)	2295 (97.1)	
Yes	232 (3.3)	99 (4.5)	64 (2.5)	69 (2.9)	
Epinephrine, n (%)					< 0.001
No	6728 (95.3)	2086 (95.9)	2442 (96.8)	2200 (93.1)	
Yes	335 (4.7)	90 (4.1)	81 (3.2)	164 (6.9)	
Phenylephrine, n (%)					< 0.001
No	6540 (92.6)	2029 (93.2)	2361 (93.6)	2150 (90.9)	
Yes	523 (7.4)	147 (6.8)	162 (6.4)	214 (9.1)	
Vasopressin, n (%)					< 0.001
No	6545 (92.7)	1980 (91)	2385 (94.5)	2180 (92.2)	
Yes	518 (7.3)	196 (9)	138 (5.5)	184 (7.8)	
Medical Procedures					
Vent, n (%)					0.53
No	1044 (14.8)	334 (15.3)	375 (14.9)	335 (14.2)	
Yes	6019 (85.2)	1842 (84.7)	2148 (85.1)	2029 (85.8)	
Intubated, n (%)					< 0.001
No	4944 (70.0)	1679 (77.2)	1870 (74.1)	1395 (59)	
Yes	2119 (30.0)	497 (22.8)	653 (25.9)	969 (41)	
Complicating disease					
COPD, n (%)					< 0.001
No	4321 (61.2)	1231 (56.6)	1521 (60.3)	1569 (66.4)	
Yes	2742 (38.8)	945 (43.4)	1002 (39.7)	795 (33.6)	
AMI, n (%)					0.144
No	4527 (64.1)	1427 (65.6)	1616 (64.1)	1484 (62.8)	
Yes	2536 (35.9)	749 (34.4)	907 (35.9)	880 (37.2)	
MC, n (%)					0.136
No	6495 (92.0)	2016 (92.6)	2299 (91.1)	2180 (92.2)	
Yes	568 (8.0)	160 (7.4)	224 (8.9)	184 (7.8)	
HepF, n (%)					0.544
No	6878 (97.4)	2116 (97.2)	2464 (97.7)	2298 (97.2)	
Yes	185 (2.6)	60 (2.8)	59 (2.3)	66 (2.8)	
vital signs					
Temperature, Mean ± SD	36.8 ± 0.5	36.7 ± 0.5	36.8 ± 0.5	36.8 ± 0.5	0.013
RespiratoryRate, Mean ± SD	19.8 ± 3.7	19.9 ± 3.7	19.9 ± 3.8	19.5 ± 3.6	< 0.001
HeartRate, Mean ± SD	83.3 ± 15.3	84.4 ± 15.8	83.1 ± 15.5	82.5 ± 14.6	< 0.001
SBP, Mean ± SD	118.7 ± 17.7	116.9 ± 18.5	119.5 ± 17.5	119.3 ± 16.9	< 0.001

Table 1 (continued)

Variables	Total ($n=7063$)	Q1 ($n=2176$)	Q2 ($n=2523$)	Q3 ($n=2364$)	P value [a]
Blood biochemical indicators					
AG, Mean ± SD	15.8 ± 4.6	17.7 ± 5.4	15.8 ± 4.0	14.1 ± 3.8	< 0.001
BUN, Mean ± SD	41.3 ± 27.8	47.9 ± 30.4	39.1 ± 26.2	37.4 ± 25.8	< 0.001
Creatinine, Mean ± SD	2.2 ± 1.9	3.0 ± 2.4	2.1 ± 1.8	1.7 ± 1.3	< 0.001
Hb, Mean ± SD	10.0 ± 2.1	10.1 ± 2.1	10.2 ± 2.2	9.6 ± 2.0	< 0.001
MCH, Mean ± SD	29.2 ± 2.8	28.9 ± 3.0	29.1 ± 2.7	29.4 ± 2.6	< 0.001
MCHC, Mean ± SD	32.1 ± 1.8	31.9 ± 1.8	32.1 ± 1.8	32.3 ± 1.7	< 0.001
MCV, Mean ± SD	90.9 ± 7.4	90.8 ± 8.1	90.6 ± 7.2	91.1 ± 7.1	0.099
Platelet, Mean ± SD	211.8 ± 96.8	227.2 ± 101.5	214.8 ± 96.2	194.3 ± 89.9	< 0.001
Potassium, Mean ± SD	4.4 ± 0.8	4.5 ± 0.9	4.4 ± 0.8	4.3 ± 0.7	< 0.001
Sodium, Mean ± SD	137.9 ± 5.4	133.9 ± 5.5	138.2 ± 3.6	141.3 ± 4.3	< 0.001
RBC, Mean ± SD	3.5 ± 0.8	3.5 ± 0.8	3.5 ± 0.8	3.3 ± 0.7	< 0.001
RDW, Mean ± SD	16.0 ± 2.4	16.4 ± 2.5	15.9 ± 2.3	15.7 ± 2.2	< 0.001
WBC, Mean ± SD	11.7 ± 8.1	11.7 ± 7.0	11.6 ± 8.1	12.0 ± 8.9	0.19
SOFA, Mean ± SD	3.6 ± 2.9	3.8 ± 3.0	3.2 ± 2.8	3.7 ± 3.0	< 0.001
APSIII, Mean ± SD	54.5 ± 21.7	57.8 ± 21.7	52.6 ± 21.0	53.6 ± 22.1	< 0.001
Hstatus, n (%)					< 0.001
survival	6203 (87.8)	1852 (85.1)	2244 (88.9)	2107 (89.1)	
death	860 (12.2)	324 (14.9)	279 (11.1)	257 (10.9)	

Abbreviations: %, weighted proportion.; Hstatus: hospital status; *CHF* congestive heart failure; *COPD* chronic obstructive pulmonary disease; *HepF* hepatic failure; *AMI* acute myocardial infarction; *APSIII* Acute Physiology III; *SOFA* Sequential Organ Failure Assessment; *SBP* systolic blood pressure; *AG* anion gap; *BUN*, blood urea nitrogen; *MCH* mean corpuscular hemoglobin; *MCHC* mean corpuscular hemoglobin concentration; *MCV* mean corpuscular volume; *RBC* red blood cell; *RDW* red blood cell distribution width; *WBC* white blood cell count Q1(≤ 98 mmol/L), Q2(98-104 mmol/L) Q3(> 104 mmol/L)

[a] *P* values of multiple comparisons were corrected by the False Discovery Rate method

[b] Q1-Q3: according to Blood Chloride

curve (solid black line) representing the relationship between the variables, and the 95% confidence interval (grey shaded area). Following adjustment for confounding factors, a statistically significant linear association was observed between Blood Chloride levels and In-hospital mortality.

Subgroup analysis

We conducted a study to assess the impact of various factors on the correlation between serum chloride levels and in-hospital mortality through subgroup analyses. We categorized participants based on age (< 60 or ≥ 60 years), gender (female or male), use of Norepinephrine (Yes or No), Dopamine (Yes or No), Epinephrine (Yes or No), Phenylephrine (Yes or No), Vasopressin (Yes or No), presence of COPD (Yes or No), melanosis coli (Yes or No), and hepatic failure (Yes or No) as stratification criteria. The primary objective was to discern trends in effect sizes, and we constructed a Forrest plot (see Fig. 3).

Our findings consistently demonstrated a significant association between serum chloride levels and in-hospital mortality across various subgroups. This result strongly supports the notion that serum chloride is independently and consistently linked to incident in-hospital mortality. Notably, the Epinephrine subgroup exhibited a noteworthy additive interaction with serum chloride (P-value for interaction < 0.05), whereas statistically significant associations were not observed in the other subgroups ($P > 0.05$).

Discussion

In this retrospective observational cohort study, we identified an association between in-hospital mortality and serum chloride level alterations among patients with diabetes and congestive heart failure (CHF). After rigorous adjustment for numerous potential confounding factors, a negative correlation between serum chloride levels and in-hospital mortality was demonstrated. The application of smooth curve fitting techniques further supported the presence of a linear relationship between serum chloride levels and in-hospital mortality. Stratified analyses consistently reaffirmed the robustness of this relationship.

Numerous clinical studies support our findings. Cuthbert et al., through regression analysis and Kaplan Meier's method, established a robust association between

Table 2 Multivariable logistic regression to assess the association of Blood Chloride with In-hospital mortality rate

	Model 1		Model 2		Model 3		Model 4		Model 5	
Blood Chloride	OR_95CI	*P* value	OR_95CI	*P* value	OR_95CI	*P* value	OR_95CI	*P* value	OR_95CI	*P* value
continuous variable	0.98 (0.97 ~ 0.99)	< 0.001	0.97 (0.96 ~ 0.98)	< 0.001	0.97 (0.96 ~ 0.98)	< 0.001	0.99 (0.97 ~ 1.01)	0.191	0.97 (0.96 ~ 0.99)	0.01
Categorical variable										
Q1(≤ 98)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2(98–104)	0.71 (0.6 ~ 0.84)	< 0.001	0.64 (0.54 ~ 0.76)	< 0.001	0.64 (0.53 ~ 0.76)	< 0.001	0.88 (0.7 ~ 1.1)	0.265	0.89 (0.7 ~ 1.13)	0.342
Q3(> 104)	0.7 (0.59 ~ 0.83)	< 0.001	0.61 (0.51 ~ 0.73)	< 0.001	0.6 (0.5 ~ 0.72)	< 0.001	0.78 (0.59 ~ 1.04)	0.095	0.73 (0.54 ~ 0.98)	0.039
P for tread		< 0.001		< 0.001		< 0.001		0.095		0.039

Abbreviations: the unit of Chloride is mmol/L, %, weighted proportion. *CHF* congestive heart failure; *COPD* chronic obstructive pulmonary disease; *HepF* hepatic failure; *AMI*, acute myocardial infarction; *APSIII* Acute Physiology III; *SOFA* sequential organ failure assessment; *SBP*, systolic blood pressure; *AG* anion gap; *BUN* blood urea nitrogen; *MCH* mean corpuscular hemoglobin; *MCHC* mean corpuscular hemoglobin concentration; *MCV* mean corpuscular volume; *RBC* red blood cell; *RDW* red blood cell distribution width; *WBC* white blood cell count, *CI* confidence interval; *OR* odds ratios, Ref: reference

Model 1: No adjustment

Model 2: Adjusted for demographic variables (sex, age, race)

Model 3: Adjusted for demographic variables, comorbidities (COPD, AMI, MC, HepF)

Model 4: Adjusted for demographic variables, comorbidities, Medical Procedures(Vent, Intubated), Medication situation(Norepinephrine Dopamine Epinephrine Phenylephrine Vasopressin),Basic vital signs(Temperature Respiratory Rate Heart Rate SBP),Blood biochemical indicators(AG BUN Creatinine, Hb MCH MCHC MCV Platelet Potassium Sodium RBC RDW WBC)

Model 5: Adjusted for demographic variables, comorbidities, Medical Procedures, Medication situation, Basic vital signs, Blood biochemical indicators, APSIII,SOFA

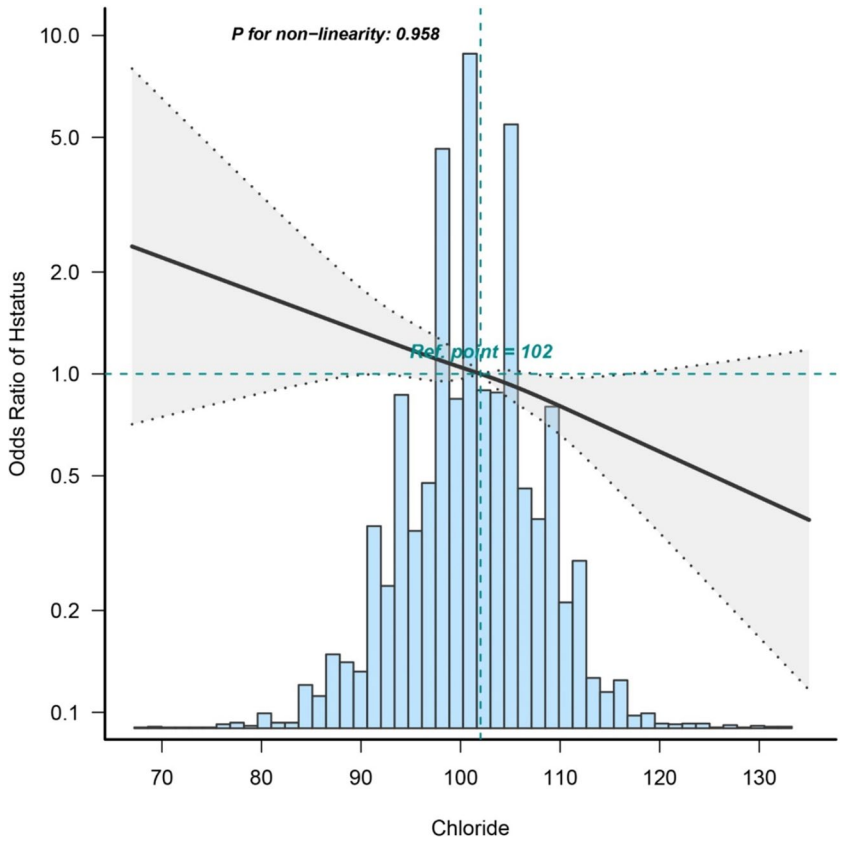

Fig. 2 Dose–Response Relationships between Blood Chloride with In-hospital mortality rate odds ratio. Solid and dashed lines represent the predicted value and 95% confidence intervals. Adjusted for demographic variables (sex, age, race), Concomitant disease(COPD,AMI,MC, HepF), Medical Procedures(Vent, Intubated), Medication situation(Norepinephrine Dopamine Epinephrine Phenylephrine Vasopressin),Basic vital signs(Temperature Respiratory Rate Heart Rate SBP),Blood biochemical indicators(AG BUN calcium Creatinine Hb MCH MCHC MCV Platelet Potassium Sodium RBC RDW WBC), APSIII,SOFA. Only 99% of the data is shown. Abbreviations: %, weighted proportion. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HepF, hepatic failure; AMI, acute myocardial infarction; APSIII, Acute Physiology III; SOFA, Sequential Organ Failure Assessment; SBP, systolic blood pressure; AG, anion gap; BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell count. CI: confidence interval; OR: odds ratios, Ref: reference

Hypochloraemia and adverse prognosis in congestive heart failure patients, suggesting its potential as a therapeutic target [28]. Similarly, Grodin et al., utilizing Cox proportional hazards models, identified an inverse relationship between serum chloride and mortality, irrespective of serum sodium levels, indicating its utility as a prognostic marker in heart failure [15]. Additionally, Justin et al. reported a 14% reduced risk of 60-day mortality, a 10% lower risk of 60-day mortality/readmission, and a 9% lower risk of 180-day mortality for every mmol/L increase in serum chloride [29]. Another study associated hyperchloremia in diabetes patients with prolonged time to diabetes resolution, increased risk of in-hospital AKI, and extended hospital LOS [17]. However, our study uniquely focuses on patients with both congestive heart failure and diabetes, distinguishing it from previous research that predominantly examined the relationship between blood chloride levels and mortality in either diabetes or heart failure patients. This targeted approach holds substantial clinical relevance, especially for specific patient populations. Our research findings reveal a negative association between serum chloride levels and in-hospital mortality in patients with both congestive heart failure and diabetes. This suggests a need for increased attention to the management of blood chloride levels in ICU patients with concomitant diabetes and heart failure, with timely adjustments using appropriate clinical measures.

This study employed smooth curve fitting and generalized additive models to assess the linear connection between serum chloride levels and in-hospital mortality in patients with congestive heart failure and diabetes, diverging from previous investigations. Subsequent subgroup analyses ensured the consistency of the main findings. The observed relationship exhibited a linear pattern, signifying that higher serum chloride levels correlate with a decreased

Subgroup	Total	Event (%)	OR (95%CI)	P for interaction
Age				
<60	1132	74 (6.5)	0.97 (0.91~1.04)	0.909
>60	5931	786 (13.3)	0.98 (0.96~1)	
Sex				
Male	3928	490 (12.5)	0.98 (0.95~1)	0.197
Female	3135	370 (11.8)	0.98 (0.95~1.01)	
Norepinephrine				
No	5349	306 (5.7)	0.96 (0.94~0.99)	0.813
Yes	1714	554 (32.3)	0.99 (0.96~1.01)	
Dopamine				
No	6831	746 (10.9)	0.98 (0.96~1)	0.401
Yes	232	114 (49.1)	0.99 (0.92~1.07)	
Epinephrine				
No	6728	728 (10.8)	0.98 (0.96~1)	0.018
Yes	335	132 (39.4)	0.97 (0.9~1.06)	
Phenylephrine				
No	6540	621 (9.5)	0.98 (0.96~1)	0.388
Yes	523	239 (45.7)	0.98 (0.93~1.03)	
Vasopressin				
No	6545	573 (8.8)	0.98 (0.95~1)	0.305
Yes	518	287 (55.4)	0.98 (0.94~1.02)	
chronic obstructive pulmonary disease				
No	4321	539 (12.5)	0.96 (0.93~0.98)	0.16
Yes	2742	321 (11.7)	1 (0.97~1.03)	
melanosis coli				
No	6495	752 (11.6)	0.98 (0.96~1)	0.747
Yes	568	108 (19)	0.95 (0.89~1.01)	
hepatic failure				
No	6878	818 (11.9)	0.98 (0.96~1)	0.136
Yes	185	42 (22.7)	1 (0.87~1.15)	

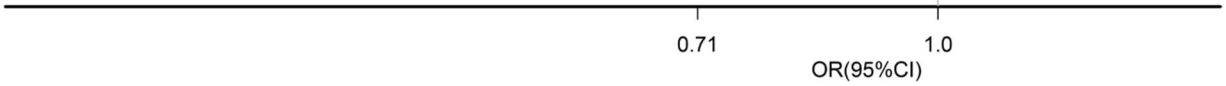

Fig. 3 Stratified analyses of the association between Blood Chloride with In-hospital mortality rate. Note: The *p* value for interaction represents the likelihood of interaction between the Blood Chloride with In-hospital mortality rate. Abbreviations: OR, odd ratio; CI, confidence interval

risk of in-hospital mortality. These findings underscore the importance of considering serum chloride levels in clinical practice. In contrast to commonly used blood routine and disease-related blood parameters for disease assessment, serum chloride stands out due to its simplicity, reliability, and convenience, rendering it an appealing option for clinical implementation.

The underlying mechanism linking serum chloride levels with in-hospital mortality risk is uncertain, but there are several potential explanations. Firstly, elevated serum chloride levels may be connected to metabolic disorders, as previous research has shown an association between serum chloride and adiponectin concentration. Increased blood chloride levels can lead to metabolic acidosis, which, in turn, reduces the level of adiponectin [30]. Adiponectin is known to play a critical cardioprotective role against inflammatory processes and decrease the risk of atherosclerosis. Therefore, the observed correlation between increased serum chloride levels and diabetes and congestive heart failure may be mediated through adiponectin concentration [31–33] Secondly, low serum chloride concentrations have been associated with recognized pathological mechanisms of in-hospital mortality in diabetes and congestive heart failure. Studies suggest that low serum chloride levels may stimulate a family of enzymes called with-no-lysine (WNK) kinases [34, 35]. These enzymes enhance the activity of Na–K-2Cl (NKCC) and Na-Cl (NC) co-transporters [36, 37], which play a role in maintaining myocyte volume and pH [38, 39]. Dysregulation of myocyte intracellular pH can lead to arrhythmias and impaired contractility [40, 41]. Additionally, cardiac chloride channels are implicated in sinoatrial pacing and arrhythmogenesis [42, 43]. Thus, there are plausible pathways through which abnormal chloride levels might influence in-hospital mortality. However, the exact underlying mechanism remains elusive.

Our study presents several notable strengths. Firstly, it explores an uncharted research area by investigating the correlation between serum chloride levels and in-hospital mortality among patients with congestive heart failure (CHF) and diabetes admitted to the ICU. Our findings establish a linear relationship between serum chloride levels and in-hospital mortality, providing a theoretical foundation for formulating targeted strategies for serum chloride level management in these patient cohorts. Moreover, the generalizability of our conclusions extends to a wider spectrum of clinical contexts. To mitigate the influence of confounding variables, we employed logistic regression analysis involving multiple models and conducted subgroup analyses with appropriate categorizations.

Nevertheless, we acknowledge some limitations within our study. It is imperative to recognize that our investigation was retrospective, inherently susceptible to inherent biases. However, we diligently adjusted for pertinent variables to enhance result accuracy. We selected serum chloride levels as the focal parameter due to its ease of measurement and practicality for clinicians. While our analytical approaches were robust, it is imperative to take into account the study's constraints. We relied on initial serum chloride levels following ICU admission and did not track their temporal fluctuations. Nevertheless, these initial levels likely offer a more precise reflection of chloride levels at the commencement of hospitalization. Furthermore, the findings should not be extrapolated exclusively to other countries or ICU facilities, given that our study was confined to the United States and a single ICU institution. Nonetheless, the substantial sample size, which is relatively representative, bolsters the credibility of our findings. For future validation, we recommend the implementation of multicenter prospective studies.

Future randomized controlled trials and systematic reviews should prioritize investigating the impact of serum chloride levels on mortality rates, specifically focusing on hospitalization, 3-month, and one-year mortality rates among individuals with comorbid diabetes and congestive heart failure. It is worth noting that the incidence of diabetes combined with heart failure is steadily rising in the ICU setting. Consequently, there remains a pressing requirement for both quantitative and qualitative research encompassing individuals diagnosed with both diabetes and congestive heart failure to enhance our existing knowledge base. Furthermore, there is a demand for more comprehensive and extended interventions and trials with substantial follow-up periods.

Conclusions

The findings of this study, based on a US nationally representative sample, lend support to the hypothesis of a negative association between serum Chloride levels and in-hospital mortality. To enhance the validity and coherence of these results, future research should employ prospective, randomized, controlled study designs.

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Author contributions KZ contributed as First authors of this manuscript. YH,FMG, and JYZ were responsible for the concept and design of the study. ZZG,JGC, BWC and MG explain the analysis. ZYH,XYQ,TYC,YFG,JYX,RH and TLZ are responsible for data recovery. KXL is the primary corresponding author. All authors critically revised the important intellectual content of the paper and approved the final draft.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. To obtain the application executable files, please contact the author Kai Zhang by email zhangkai7018@jlu.edu.cn.

Declarations

Ethics approval and consent to participate The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), and informed consents were exempted due to patients' data were anonymized before the data were obtained. We also complied with all relevant ethical regulations regarding the use of the data in our study. All reports adhered to the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology and the Declaration of Helsinki.

Approval date of registry and the registration No. of the study/trial N/A

Animal studies N/A

Conflict of interest The authors declare no conflict of interest.

Competing interests The authors declare that they have no competing interests.

References

1. Rani R, Dahiya S, Dhingra D, Dilbaghi N, Kaushik A, Kim KH, et al. Antidiabetic activity enhancement in streptozotocin + nicotinamide-induced diabetic rats through combinational polymeric nanoformulation. Int J Nanomedicine. 2019;14:4383–95.
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
3. El Hajj MC, Ninh VK, El Hajj EC, Bradley JM, Gardner JD. Estrogen receptor antagonism exacerbates cardiac structural and functional remodeling in female rats. Am J Physiol Heart Circ Physiol. 2017;312(1):H98-h105.
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.
5. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007;115(25):3213–23.
6. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. J Am Coll Cardiol. 2010;55(4):300–5.
7. Kamalesh M. Diabetes and prognosis: are systolic and diastolic heart failure different? Heart. 2009;95(3):178–9.
8. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, et al. Type 2 diabetes mellitus and heart failure: A scientific statement from the American heart association and the heart failure society of America: This statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation. 2019;140(7):e294–324.
9. Nassif M, Kosiborod M. Effect of glucose-lowering therapies on heart failure. Nat Rev Cardiol. 2018;15(5):282–91.
10. Cai D, Xiao T, Zou A, Mao L, Chi B, Wang Y, et al. Predicting acute kidney injury risk in acute myocardial infarction patients: An artificial intelligence model using medical information mart for intensive care databases. Front Cardiovasc Med. 2022;9:964894.
11. Bhave G, Neilson EG. Body fluid dynamics: back to the future. J Am Soc Nephrol. 2011;22(12):2166–81.
12. Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? Eur J Intern Med. 2012;23(3):203–11.
13. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: Chloride in critical illness. Crit Care. 2010;14(4):226.
14. Soussi S, Ferry A, Chaussard M, Legrand M. Chloride toxicity in critically ill patients: What's the evidence? Anaesth Crit Care Pain Med. 2017;36(2):125–30.
15. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, et al. Prognostic role of serum chloride levels in acute decompensated heart failure. J Am Coll Cardiol. 2015;66(6):659–66.
16. Testani JM, Hanberg JS, Arroyo JP, Brisco MA, Ter Maaten JM, Wilson FP, et al. Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure. Eur J Heart Fail. 2016;18(6):660–8.
17. Goad NT, Bakhru RN, Pirkle JL, Kenes MT. Association of hyperchloremia with unfavorable clinical outcomes in adults with diabetic ketoacidosis. J Intensive Care Med. 2020;35(11):1307–13.
18. Tang R, Peng J, Wang D. central venous pressure measurement is associated with improved outcomes in patients with or at risk for acute respiratory distress syndrome: an analysis of the medical information mart for intensive care IV database. Front Med (Lausanne). 2022;9:858838.
19. Pfohl SR, Foryciarz A, Shah NH. An empirical characterization of fair machine learning for clinical risk prediction. J Biomed Inform. 2021;113:103621.
20. Wong AI, Charpignon M, Kim H, Josef C, de Hond AAH, Fojas JJ, et al. Analysis of discrepancies between pulse oximetry and arterial oxygen saturation measurements by race and ethnicity and association with organ dysfunction and mortality. JAMA Netw Open. 2021;4(11):e2131674.
21. Biswas A, Parikh CR, Feldman HI, Garg AX, Latham S, Lin H, et al. Identification of patients expected to benefit from electronic alerts for acute kidney injury. Clin J Am Soc Nephrol. 2018;13(6):842–9.
22. Khan AM, Chiasakul T, Redd R, Patell R, McCarthy EP, Neuberg D, et al. Survival outcomes with warfarin compared with direct oral anticoagulants in cancer-associated venous thromboembolism in the United States: A population-based cohort study. PLoS Med. 2022;19(5):e1004012.
23. Jiménez KM, Pereira-Morales AJ, Adan A, Forero DA. Telomere length and childhood trauma in Colombians with depressive symptoms. Braz J Psychiatry. 2019;41(3):194–8.
24. Dashdorj NJ, Dashdorj ND, Mishra M, Danzig L, Briese T, Lipkin WI, et al. Molecular and serologic investigation of the 2021 COVID-19 case surge among vaccine recipients in Mongolia. JAMA Netw Open. 2022;5(2):e2148415.
25. Tang Y, Chen Q, Liang B, Peng B, Wang M, Sun J, et al. A retrospective cohort study on the association between early coagulation disorder and short-term all-cause mortality of critically ill patients with congestive heart failure. Front Cardiovasc Med. 2022;9:999391.
26. Zhong L, Xie B, Ji XW, Yang XH. The association between albumin corrected anion gap and ICU mortality in acute kidney injury patients requiring continuous renal replacement therapy. Intern Emerg Med. 2022;17(8):2315–22.
27. Wu B, Guo Y, Yang HH, Gao QG, Tian Y. Predicting bone metastasis risk based on skull base invasion in locally advanced nasopharyngeal carcinoma. Front Oncol. 2022;12:812358.
28. Cuthbert JJ, Pellicori P, Rigby A, Pan D, Kazmi S, Shah P, et al. Low serum chloride in patients with chronic heart failure: clinical associations and prognostic significance. Eur J Heart Fail. 2018;20(10):1426–35.
29. Grodin JL, Sun JL, Anstrom KJ, Chen HH, Starling RC, Testani JM, et al. Implications of serum chloride homeostasis in acute heart failure (from ROSE-AHF). Am J Cardiol. 2017;119(1):78–83.

30. Disthabanchong S, Niticharoenpong K, Radinahamed P, Stitchantrakul W, Ongphiphadhanakul B, Hongeng S. Metabolic acidosis lowers circulating adiponectin through inhibition of adiponectin gene transcription. Nephrol Dial Transplant. 2011;26(2):592–8.
31. Liu W, Zhou X, Li Y, Zhang S, Cai X, Zhang R, et al. Serum leptin, resistin, and adiponectin levels in obese and non-obese patients with newly diagnosed type 2 diabetes mellitus: A population-based study. Medicine (Baltimore). 2020;99(6):e19052.
32. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci. 2017;18(6):1321.
33. Hjort R, Ahlqvist E, Andersson T, Alfredsson L, Carlsson PO, Grill V, et al. Physical activity, genetic susceptibility, and the risk of latent autoimmune diabetes in adults and type 2 diabetes. J Clin Endocrinol Metab. 2020;105(11):e4112–23.
34 Piala AT, Moon TM, Akella R, He H, Cobb MH, Goldsmith EJ. Chloride sensing by WNK1 involves inhibition of autophosphorylation. Sci Signal. 2014;7(324):ra41.
35. Bazúa-Valenti S, Chávez-Canales M, Rojas-Vega L, González-Rodríguez X, Vázquez N, Rodríguez-Gama A, et al. The effect of WNK4 on the Na+-Cl- cotransporter is modulated by intracellular chloride. J Am Soc Nephrol. 2015;26(8):1781–6.
36. 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(12):1150–8.
37. 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(11):3403–11.
38. 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(1):89–114.
39. Adkins GB, Curtis MJ. Potential role of cardiac chloride channels and transporters as novel therapeutic targets. Pharmacol Ther. 2015;145:67–75.
40. Orchard CH, Cingolani HE. Acidosis and arrhythmias in cardiac muscle. Cardiovasc Res. 1994;28(9):1312–9.
41. Orchard CH, Kentish JC. Effects of changes of pH on the contractile function of cardiac muscle. Am J Physiol. 1990;258(6 Pt 1):C967–81.
42. Huang ZM, Prasad C, Britton FC, Ye LL, Hatton WJ, Duan D. Functional role of CLC-2 chloride inward rectifier channels in cardiac sinoatrial nodal pacemaker cells. J Mol Cell Cardiol. 2009;47(1):121–32.
43. Duan DY, Liu LL, Bozeat N, Huang ZM, Xiang SY, Wang GL, et al. Functional role of anion channels in cardiac diseases. Acta Pharmacol Sin. 2005;26(3):265–78.