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Article

The Association between the Hypochloremia and Mortality in Intensive Care Unit (ICU) Patients with Chronic Heart Failure

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Abstract: Objective: To explore the association between hypochloremia and mortality in critically ill patients with chronic heart failure (CHF). Methods: This is a retrospective cohort study from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database of patients with CHF diagnosed according to ICD-9 or ICD-10. Patients were divided into three groups according to serum chloride values. A multivariable logistic regression analysis was used to investigate the relationship between hypochloremia and short-term mortality. Results: A total of 2103 patients with CHF were enrolled in our study. The 30-day mortality was 6.7%. After adjusting for confounders, the 30-day mortality risks of the hypochloremia group were significantly higher than that of the group with normal serum chloride (OR 2.23, 95% CI 1.27–3.92, $p = 0.005$). Hypochloremia was consistently associated with increased mortality in patients that were older or had sepsis. Conclusion: Hypochloremia is associated with increased mortality in intensive care patients critically ill with CHF.

Keywords: hypochloremia; chronic heart failure (CHF); mortality; intensive care unit (ICU); the Medical Information Mart for Intensive Care-IV (MIMIC-IV)

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1. Introduction

Chloride accounts for 70% of the negative ion content in the human body [1]. Chloride and sodium play important roles in maintaining body fluid osmotic pressure, acid-base balance, and electrical neutrality [2]. Chlorides are often present and included in biochemical tests of critically ill patients, but rarely cause concern. In critically ill patients, alterations in chloride balance, both absolute and relative to hyponatremia, can alter acid-base status, cell biology, renal function, and hemostatic effects [3]. In the general intensive care unit (ICU), studies have reported incidence rates from 6.7% to 35.1% for hypochloremia [4–7]. Among patients with heart failure, the reported incidence rate of hypochloremia ranges from 7.4% to 23% [8–12]. The recently discovered with-no-lysine/K (WNK) protein kinase includes intracellular chloride-sensing proteins whose phosphorylation and activation occur with hypochloremia [13,14]. WNK protein kinase plays an important role in regulating sodium chloride homeostasis and the renin-angiotensin-aldosterone system [15]. Recently, it has been found that the gene encoding the voltage-sensitive chloride channel (CLCNKA) may be associated with renal sodium reabsorption [16]. These potential associations suggest that the chloride channels may have an effect on chronic heart failure. Due to the complexity of the ICU patient's situation, patients may experience in-hospital worsening of heart failure (WHF) and become at greater risk of adverse outcomes compared with patients who do not experience this [17]. The existing research investigates the association between serum chloride and mortality in patients with chronic heart failure in the ICU, as no data exist on hypochloremia in ICU patients with chronic heart failure.

2. Methods

2.1. Data Source

We obtained all data from the Medical Information Mart for Intensive Care IV (MIMIC-IV), a single-center, freely accessible database of admission information collected from 2008 to 2019 at Beth Israel Deaconess Medical Center in Boston [18]. We completed the online course and passed the online exams (no. 45574629) required to gain access to the database.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria for the study were patients with chronic heart failure (CHF), defined as ICD-9 codes 42,822, 42,832 and 42,842 or ICD10 codes I5022, I5032 and I5042. The exclusion criteria were patients with malignancy, patients with cerebral infarction or cerebral hemorrhage, and patients receiving dialysis. For patients with multiple ICU admissions, only data from the first ICU index admission were included.

2.3. Data Collection

Data were extracted from MIMIC-IV using structured query language (SQL) and Navicat Premium (version 15.0), searching for records that included age, sex, race, type of admission, comorbidity, blood routine, blood biochemistry, sequential organ failure assessment (SOFA) score, heart failure medication and vasopressor use. In the collected data, less than 10% of any variable had missing values. Single imputation was used to impute missing values.

2.4. Primary and Secondary Outcomes

The 30-day mortality was the primary outcome; length of hospital stay and length of stay in the ICU as secondary outcomes.

2.5. Statistical Analysis

Categorical variables are presented as percentages, and continuous variables were presented as means (±standard deviation [SD] or inter-quartile range [IQR]). All variables were compared with a Student's *t*-test, Chi-square test, Wilcoxon signed-rank test, or Kruskal–Wallis test. A two-tailed *p*-value of less than 0.05 was considered statistically significant. Multiple logistic regression analysis and smooth curve fitting were performed to test the independent effect of hypochloremia on in-hospital mortality for all models. Confounders were selected for inclusion in models on the basis of p-values < 0.05 in univariate analyses; these potential confounders were judged by clinical expertise and adjusted. Baseline variables considered to be clinically relevant or to have a univariate relationship with the outcome ($p < 0.10$) were entered as covariates in a multiple logistic regression model; these included age, sex, heart rate, mean arterial pressure, respiratory rate, SpO2,white blood cell count, hemoglobin, serum sodium, serum potassium, serum creatinine, blood bicarbonate, NT-pro-BNP, medication prescribed for heart failure, vasopressor use, comorbidities, and SOFA score. Subgroup analyses were performed after grouping patients according to age, sex, presence or absence of reduced left ventricle ejection fraction, and presence or absence of sepsis. All statistical analyses were performed with using Stata v. 15.0 software.

3. Results

3.1. Baseline Characteristics

The MIMIC-IV database includes 12,911 patients with CHF, of which 4553 were excluded because of malignancy; 167 were excluded because of cerebral hemorrhage, 732 were excluded because of cerebral infarction, and 600 were excluded because of dialysis status. After exclusion of outliers and missing values (4746 patients), 2103 patients were included in this analysis (Figure 1), including 1956 survivors and 147 non-survivors, with an in-hospital mortality of 7.0%. The mean age of patients was 72.6 ± 14.1 years; 1126 patients were male (53.5%). The survival group tended to have lower white blood cell count,

hemoglobin, serum creatinine, N-terminal-pro hormone B-type natriuretic peptide (NT-pro-BNP), SOFA score, increased use of drugs for heart failure, and less use of vasoactive drugs. These variables may be confounded with hypochloremia and were thus controlled for in subsequent analyses.

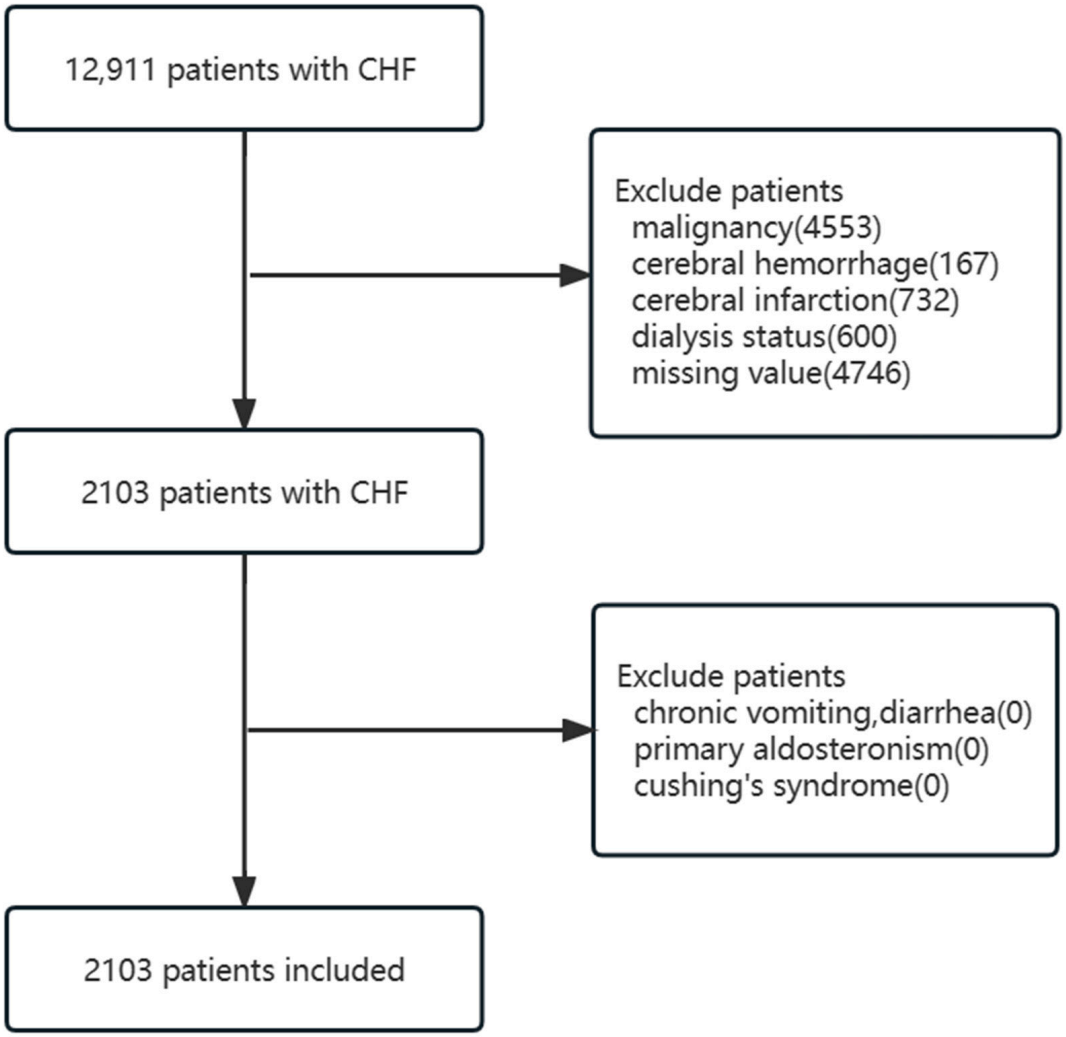

Figure 1. The flow chart of the study.

3.2. Relationship between Baseline Level of Serum Chloride and Outcomes

Univariate analyses of in-hospital mortality are shown in Table 1.

Table 1. Baseline characteristics of the total cohort, survivors, and non-survivors.

Variable	Total *n* (*n* = 2103)	Survivors (*n* = 1956)	Non-Survivors (*n* = 147)	*p*
Age (years)	72.6 ± 14.1	72.0 ± 14.1	79.7 ± 12.1	<0.001
Male (*n* (%))	1126 (53.5)	1049 (53.6)	77 (52.4)	0.770
Heart rate (bpm)	83.3 ± 16.4	83.1 ± 16.3	86.1 ± 17.0	0.0347
MAP (mmHg)	75.7 ± 10.5	76.0 ± 10.3	71.5 ± 11.4	<0.001
RR (bpm)	19.8 ± 3.8	19.7 ± 3.7	21.3 ± 4.4	<0.001
SPO2 (%)	96.5 ± 2.2	96.6 ± 2.0	95.7 ± 3.4	<0.001
Glucose (mg/dL)	150.6 ± 55.4	150.1 ± 54.1	157.7 ± 70.1	0.1092
Wbc (10^9/L)	11.9 ± 9.7	11.7 ± 9.7	14.0 ± 8.9	0.0065

Table 1. *Cont.*

Variable	Total *n* (*n* = 2103)	Survivors (*n* = 1956)	Non-Survivors (*n* = 147)	*p*
Hemoglobin (g/dL)	11.1 ± 2.3	11.1 ± 2.3	10.5 ± 2.1	0.0012
Platelet (10^9/L)	219.1 ± 99.5	220.6 ± 98.8	199.4 ± 107.0	0.0128
Sodium (mmol/L)	137.7 ± 5.3	137.7 ± 5.2	138.1 ± 6.6	0.4038
Potassium (mmol/L)	4.4 ± 0.8	4.3 ± 0.8	4.6 ± 1.0	0.0004
Bicarbonate (mmol/L)	24.2 ± 5.2	24.3 ± 5.1	22.9 ± 6.5	0.0019
Aniongap (mmol/L)	15.5 ± 4.1	15.3 ± 3.9	17.9 ± 5.5	<0.001
Creatinine (mg/dL)	1.6 ± 1.2	1.5 ± 1.1	2.3 ± 1.8	<0.001
Bun (mg/dL)	34.1 ± 24.8	32.9 ± 23.8	50.1 ± 32.1	<0.001
NT-pro-BNP (pg/mL)	2819.0 (944.0–7485.0)	2771.5 (944.5–944.5)	4798.0 (940.0–13,113.0)	0.0041
SOFA score	5.0 ± 3.4	4.7 ± 3.2	9.2 ± 3.9	<0.001
ACEI (%)	1262 (60.0)	1200 (61.4)	62 (42.2)	<0.001
ARB (%)	552 (26.3)	526 (26.9)	26 (17.7)	0.014
β-blocker (%)	1795 (85.4)	1683 (86.0)	112 (76.2)	0.001
Spirolactone (%)	604 (28.7)	575 (29.4)	29 (19.7)	0.012
Digoxin (%)	413 (19.6)	392 (20.0)	21 (14.3)	0.090
Loop diuretic (%)	1987 (94.5)	1855 (94.8)	132 (89.8)	0.010
Hiazide diuretic (%)	319 (15.2)	307 (15.7)	12 (8.2)	0.014
CAD (%)	1389 (66.1)	1309 (66.9)	80 (54.4)	0.002
Hypertension (%)	1325 (63.0)	1250 (63.9)	75 (51.0)	0.002
Diabetes (%)	1128 (53.6)	1059 (54.1)	69 (46.9)	0.091
AF (%)	1255 (59.7)	1155 (59.1)	100 (68.0)	0.032
Sepsis (%)	680 (32.3)	602 (30.8)	78 (53.1)	<0.001
Dopamine (%)	110 (5.2)	91 (4.7)	19 (12.9)	<0.001
Dobutamine (%)	81 (3.9)	58 (3.0)	23 (15.7)	<0.001
Norepinephrine (%)	430 (20.5)	344 (17.6)	86 (58.5)	<0.001

MAP—mean arterial pressure. RR—respiratory rate. SPO2—saturation of arterial blood. Wbc—white blood cell count.NT-pro-BNP—N-terminal pro-Brain Natriuretic Peptide.SOFA score—Sequential Organ Failure Assessment score. ACEI—angiotensin-converting enzyme inhibitor. ARB—angiotensin receptor blockers. CAD—coronary artery disease. AF—atrial fibrillation.

We divided patients into three groups according to baseline serum chloride levels and compared the clinical outcomes of the subjects among groups (Table 2).

Table 2. Outcomes of patients with chronic heart failure for different levels of baseline chloride.

Variable	All Patients	Serum Chloride (mmol/L) Median (P25, P75)			*p*-Value
		<96 92 (89, 94)	≥96, <108 102 (99, 104)	≥108 110 (109, 112)	
n	2103	328	1437	338	
In-hospital mortality	147 (7.0%)	36 (11.0%)	86 (6.0%)	25 (7.4%)	0.006
30-day mortality	140 (6.7%)	35 (10.7%)	83 (5.8%)	22 (6.5%)	0.006
Time in hospital (days)	7.7 (4.7, 12.7)	7.9 (4.9, 12.9)	7.2 (4.5, 12.3)	8.7 (5.0, 13.6)	0.013
Time in ICU (days)	2.1 (1.2, 4.0)	2.2 (1.2, 4.2)	2.0 (1.1, 3.8)	2.3 (1.3, 4.5)	0.002

The hypochloremia group (<96 mmol/L) had higher in-hospital mortality and 30-day mortality (p = 0.006 and 0.006, respectively), and longer stays in the hospital and in the ICU (p = 0.013 and p = 0.002, respectively) than the normal serum chloride group. Patients with hyperchloraemia (>108 mmol/L) had longer stays than hypochloraemic patients, with a U-shaped association with LOS/ICU LOS. Smooth curve fitting was used to show the association between baseline chloride and the risk of in-hospital mortality (Figure 2).

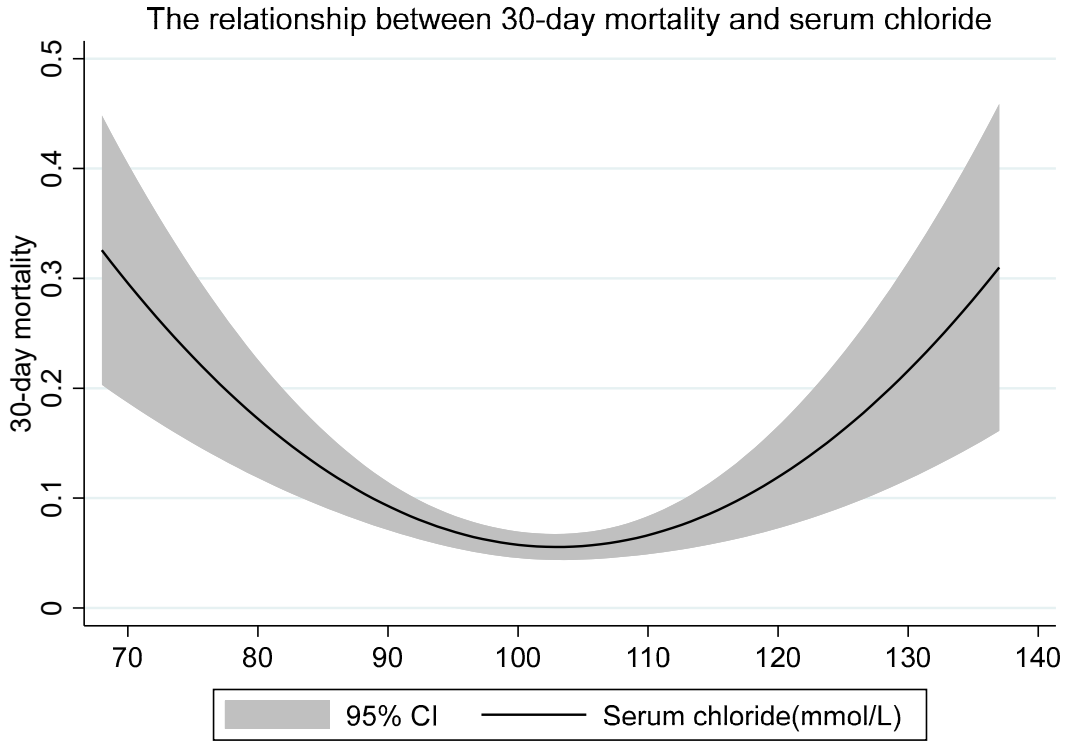

Figure 2. Smoothed curve fit for the relationship between chloride and the risk of 30-day mortality.

In the multiple logistic regression analyses, after adjusting for listed clinical confounders, patients with a low baseline serum chloride (<96 mmol/L) had higher 30-day mortality (OR: 2.23, 95% CI: 1.27–3.92, $p = 0.005$) compared to the adjusted-model normal (reference) group (96 < serum chloride $\leq$ 108; Table 3). Serum chloride levels that were higher than normal did not significantly affect mortality rates (Table 3).

Table 3. Multiple logistic regression analysis of serum chloride levels' effects on mortality in Table 2.

30-Day Mortality	Model-1			Model-2			Model-3		
Serum Chlorion (mmol/L)	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
<96	2.07	(1.36, 3.16)	0.001	1.98	(1.18, 3.31)	0.009	2.23	(1.27, 3.92)	0.005
≥96, <108	1.0		reference	1.0		reference	1.0		reference
<108	1.11	(0.68, 1.82)	0.665	1.01	(0.57, 1.79)	0.967	0.73	(0.39, 1.37)	0.331

Model 1: model that includes age and gender as covariates. Model 2: model that includes model 1 covariates plus HR, MAP, RR, SpO2, hemoglobin, sodium, potassium, creatinine, NT-pro-BNP, CAD, hypertension, atrial fibrillation, ACEI, ARB, spirolactone and beta-blocker use. Model 3: model that includes all covariates in model 2 model plus the covariates white blood cell count, norepinephrine and SOFA score.

3.3. Subgroup Analysis

Subgroup analyses of the association between baseline serum chloride and 30-day mortality are shown in Table 4, and were performed according to age, sex, presence or absence of reduced left ventricle ejection fraction, and presence or absence of sepsis. An association between serum chloride and risk of 30-day mortality varied between subgroups, present only for patients ≥65 years-old and patients with sepsis.

Figure 3 shows the OR and 95% CI for the two groups (for patients ≥65 years-old and patients with sepsis).

Table 4. Multivariable logistic regression analyses for subgroups.

		n	Hypochloremia Group			Normal Serum Chlorion Group Reference	Hyperchloremia Group		
			OR	**95% CI**	***p*-Value**		**OR**	**95% CI**	***p*-Value**
Age (years)	<65	582	2.51	(0.30, 21.27)	0.400	1.0	0.06	(0.00, 2.18)	0.123
	≥65	1521	2.29	(1.25, 4.20)	0.007	1.0	0.81	(0.42, 1.55)	0.523
Gender	Male	1126	2.16	(0.98, 4.72)	0.055	1.0	0.55	(0.21, 1.42)	0.217
	Female	977	2.31	(0.99, 5.37)	0.052	1.0	0.94	(0.40, 2.24)	0.893
CHF	HFrEF	1127	2.02	(0.84, 4.90)	0.118	1.0	0.76	(0.28, 2.06)	0.596
	HFpEF	976	2.07	(0.96, 4.48)	0.064	1.0	0.69	(0.30, 1.57)	0.376
Sepsis	Without sepsis	1423	1.95	(0.91, 4.19)	0.087	1.0	1.19	(0.58, 2.41)	0.635
	With sepsis	680	2.47	(1.21, 5.05)	0.013	1.0	0.51	(0.21, 1.25)	0.141

CHF—chronic heart failure. HFrEF—Heart failure with reduced ejection fraction. HFpEF—Heart failure with preserved ejection fraction.

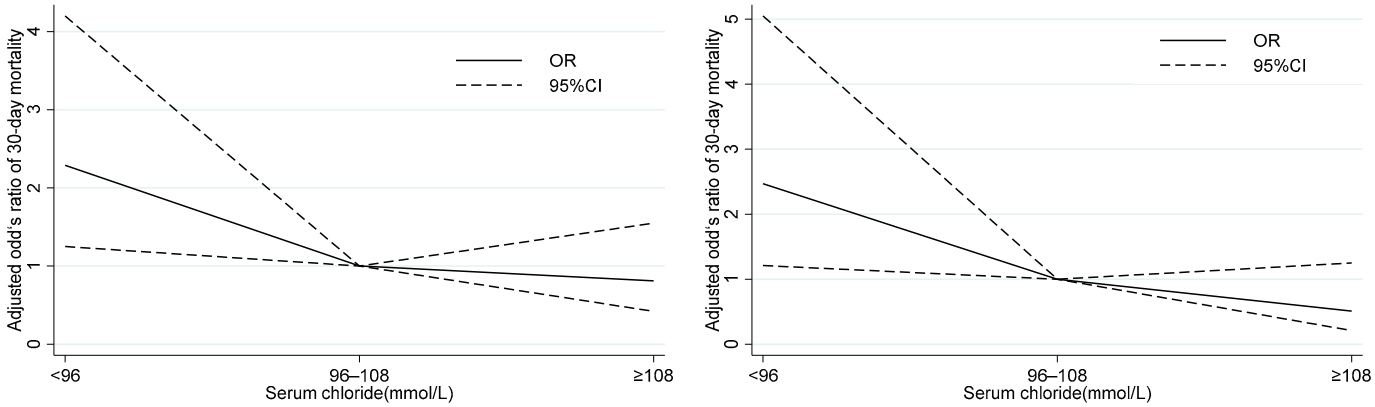

Figure 3. Adjusted OR of hospital mortality for during ICU stay in subgroups. After adjusting the age, gender, HR, MAP, RR, SpO2,hemoglobin, sodium, potassium, creatinine, NT-pro-BNP, CAD, hypertension, atrial fibrillation, ACEI, ARB, spirolactone, beta-blocker use, white blood cell count, norepinephrine and SOFA score, in patients aged 65 years OR older, chronic heart failure patients with hypochloremia had a higher OR than the normal and hyperchlorinated groups (**left**), and chronic heart failure patients with hypochloremia had a higher OR than the normal and hyperchlorinated groups (**right**) in patients with sepsis.

4. Discussion

Our study reveals an association between hypochloremia and short-term mortality in ICU patients with CHF. Patients with hypochloremia had a higher short-term mortality than those with normal serum chloride. In accordance with this, several previous studies on the association between hypochloremia and mortality in patients with CHF have found that hypochloremia is independently associated with mortality in patients with CHF [8–12,17]. A study by Cuthbert, Joseph et al. showed that in chronic heart failure, patients with hypochloremia, the hypochloremia group, regardless of whether sodium was low or normal had a markedly worse prognosis than patients with isolated low sodium or those with both normal sodium and chloride. At follow-up one year later, death from end-stage heart failure was more common in patients with hypochloremia [8]. Yang Zhang et al. found that hospital admission serum chloride concentration was independently and negatively correlated with long-term mortality in the Han population. This relationship remained independent of sodium concentration after multivariate risk adjustment for age, being male, history of diabetes, LVEF, loop diuretic use, beta blocker use, ACEI or ARB use,

eGFR, and NT-proBNP [19]. Justin L. Grodin et al. found lower serum chloride levels were independently and gradually associated with an increased risk of death in patients with chronic heart failure at 5-year all-cause mortality follow-up, as well as in multivariate models [10].

However, while chlorine abnormalities in ICU patients have attracted considerable attention, CHF in intensive care patients has not been adequately studied to date. Currently, little is known about chloride channels compared to sodium, potassium, and calcium channels. Chloride is found in $GABA_A$ channels, calcium-activated chloride channels and voltage-gated chloride channels, among others [3]. Of these, volume-sensitive chloride channels are involved in the volume regulation of cells. Chloride ions exposed to the stimulation of hypotonic media are egressed through these channels, resulting in a balance of intracellular and extracellular tension [20], and such channels play a role in apoptosis [21] and may be associated with sepsis [22]. Hyperchloremia or hypochloremia caused by disease processes and clinical manipulations are common in ICU and are consistently associated with sodium [3], such as diuretic treatment, significant gastric drainage, vomiting, chronic respiratory acidosis and an increase in water over chloride [3]. The use of intravenous chlorine-rich fluids may interfere with the research results.

In patients over 65 years of age, hypochloremia is significantly associated with 30-day mortality for patients with CHF in the ICU. The elderly are more likely to have electrolyte disturbances and unique pathophysiological states for several reasons. First, cardiac physiologic structure changes with age. Some diseases that increase in incidence with age (such as diabetes, hypertension, etc.) may lead to hardening and diastolic dysfunction of the heart muscle Second, older patients have an increased frequency of atherosclerosis and arteriosclerosis, which are associated with progression of cardiovascular disease, limited physical activity, and a poorer general physical condition. Atherosclerosis can also lead to more arrhythmias and other complications Third, non-adherence to diet or medication in patients with CHF is a common factor leading to decompensation in elderly patients the complexity of the treatment regimen, the side effects of medications, and the patient's perception of the need for treatment can also affect patient adherence.

A statistically significant association was found between hypochloremia and mortality in ICU heart failure patients with sepsis. ICU patients have particular complexity. Typically, a large volume of fluid is present in ICU patients, and its effect on chloride could not be quantified in the current study. In addition, a considerable percentage of patients in ICU have sepsis, which can lead to sepsis-induced myocardial dysfunction. In patients with sepsis, left ventricular systolic dysfunction is considered a reversible response of cardiac function that is more prone to electrolyte disturbances, which may affect left ventricular ejection fraction. Further clinical and basic research are needed.

Our study has six limitations. First, the results of this study are associative and do not imply causality. Thus, the underlying molecular and physiological mechanisms need to be further studied and elucidated. Second, the effect of whether or not patients received fluid resuscitation before ICU admission was not considered. Third, a big limitation is that we do not have data on intravenous fluids in these patients, which may interfere with the results. Fourth, multiple subgroup analyses may increase the risk of false-positive results. Fifth, the retrospective design does not make it possible to adjust for all confounders. Finally, this is a single-center study, and the results need to be validated with multicenter trials.

5. Conclusions

In conclusion, our investigation suggests an association between hypochloremia and short-term mortality in patients with CHF in the ICU. Patients with hypochloremia have greater short-term mortality compared to patients with normal serum chloride. This relationship needs to be further validated in other populations, and the mechanisms underlying these associations need to be further investigated. Further clinical studies are needed to confirm whether clinical intervention to increase serum chloride levels can improve prognoses.

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Institutional Review Board Statement: MIMIC-IVwas deidentified, and patient identifiers were removed according to the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provision.Therefore, no ethical approval is required.

Informed Consent Statement: Patient consent was waived because MIMIC-IV was deidentified, and patient identifiers were removed according to the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provision.

Data Availability Statement: The datasets are available in Physionet accessed on 10 January 2021 (https://physionet.org/content/mimiciv/1.0/).

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Conflicts of Interest: Ethics approval and consent to participate was received. The MIMIC-IV database was approved by the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA), and consent was obtained for the original data collection. The authors declare no conflict of interest.

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