Relationship between serum chloride and prognosis in non-ischaemic dilated cardiomyopathy: a large retrospective cohort study

Xinyi Li, Xiaonan Zhang, Yaoxin Liu, Fen Shu, Sisi Shao, Ning Tan, Lei Jiang

ABSTRACT

Objectives Serum chloride has a unique homeostatic role in modulating neurohormonal pathways. Some studies have reported that hypochloremia has potential prognostic value in cardiovascular diseases; thus, we aimed to investigate the association of baseline serum chloride with clinical outcomes in elderly patients with non-ischaemic dilated cardiomyopathy (NIDCM).

Design Retrospective study.

Setting and participant A total of 1088 patients (age ≥60 years) diagnosed with NIDCM were enrolled from January 2010 to December 2019.

Results Logistic regression analyses showed that serum chloride was significantly associated with in-hospital death. Receiver operating characteristic (ROC) curve analyses showed that serum chloride had excellent prognostic ability for in-hospital and long-term death (area under the curve (AUC)=0.690 and AUC=0.710, respectively). Kaplan-Meier survival analysis showed that the patients with hypochloremia had worse prognoses than those without hypochloremia (log-rank \( \chi^2 = 56.69, p<0.001 \)). After adjusting for age, serum calcium, serum sodium, left ventricular ejection fraction, lg NT-proBNP and use of diuretics, serum chloride remained an independent predictor of long-term death (HR 0.934, 95% CI 0.913 to 0.954, p<0.001).

Conclusions Serum chloride concentration was a prognostic indicator in elderly patients with NIDCM, and hypochloremia was significantly associated with both in-hospital and long-term poor outcomes.

INTRODUCTION

Non-ischaemic dilated cardiomyopathy (NIDCM) is defined as left ventricle (LV) enlargement and global systolic function impairment (left ventricular ejection fraction (LVEF)<45%) in the absence of coronary artery disease or increased loading conditions.1 and NIDCM is one of the most common causes of heart failure (HF) and the most common indicator for heart transplantation, with an estimated prevalence of 40 per 100,000 individuals and an annual incidence of 7 per 100,000 individuals.2,3 Currently, no effective treatments can prevent the progression of NIDCM to HF,4 and patients often suffer from refractory HF and even sudden cardiac death (SCD) and could benefit from cardiac transplantation.5,6 This condition places a heavy financial burden on global healthcare systems. Patients with NIDCM have an increased risk of life-threatening arrhythmia and HF, and the stratification of their risk is a real challenge for clinicians.7

Previous research has shown that a few variables, such as reduced LVEF and elevated levels of brain natriuretic peptide,8 have been associated with poor outcomes of patients (age <60 years) with dilated cardiomyopathy (DCM). Although there have been many studies on DCM,1–3,9 to the best of our knowledge, there have been no previous studies on risk factors for elderly patients. Recently, several studies showed that serum chloride has unique homeostatic roles in modulating neurohormonal pathways, regulating tubular diuretic-sensitive channels and influencing renal salt handling,10,11 and hypochloremia was found to have a potential prognostic role in HF.12–14 Thus, in this study, we assessed the association of serum chloride with clinical outcomes in elderly patients with NIDCM.
METHODS

Study population
According to the scientific statement established by the American Heart Association, NIDCM is defined as ventricu-
lar dilatation and systolic dysfunction excluding vascular
diseases such as coronary heart disease and myocardial
infarction.8 For this study, we retrospectively investigated
1088 patients (age ≥60 years) admitted for NIDCM to
Guangdong Provincial People’s Hospital (Guangzhou,
China) from January 2010 to December 2019.

Patient and public involvement
No patient was involved.

Data source
Baseline characteristics, medical history and laboratory
results were collected from the electronic medical data-
base. Clinical information was collected from an elec-
tronic case report form by one researcher and randomly
confirmed by another researcher. Basal serum chloride
samples were collected the morning after admission.
Serum chloride was measured by the bromocresol green
method using a Beckman Coulter AU5821 or AU5831
(Beckman Coulter, California, USA). The LVEF was deter-
mined using Simpson’s biplane method. Linear internal
measurements of the LV and its walls were performed in
the parasternal view.

Definition and endpoints
Serum chloride of <96 mmol/L on admission was defined
as hypochloremia.10 The patients were followed up
through telephone calls or via a review of their outpatient
clinic records in 2021. The endpoints of this study were
in-hospital death and all-cause death during follow-up.

Statistical analysis
Continuous variables are presented as the mean±SD and
were compared by one-way analysis of variance. Cate-
gorical variables are expressed as numbers, n (proport-
ions, %) and were compared through Pearson’s $\chi^2$
tests. Missing values were excluded from the analysis. Kaplan-
Meier survival curves were drawn to compare the cumula-
tive event rates among the groups and were compared by
the log-rank test. Receiver operating characteristic (ROC)
curves were drawn to assess the prognostic value of serum
chloride. Logistic regression analyses were used to eval-
uate the association of serum chloride with in-hospital
mortality. Multivariate Cox proportional hazard regres-
sion models were built to adjust for possible confounders
at baseline and evaluate the association of serum chloride
with long-term mortality. All analyses were performed
using SPSS software V.26.0, and p values were two-sided
with a significance level of 0.05.

RESULTS
A total of 1088 patients (711 men and 377 women) were
included in this study, and 167 patients were older than
75 years old. A total of 506 patients died, and 30 were lost
during a median follow-up of 67±1.8 months. All patients
were divided into two groups according to the serum
chloride concentrations on admission: hypochloremia
(<96 mmol/L) and nonhypochloremia (≥96 mmol/L).

First, detailed baseline characteristics for this cohort
showed that sex composition and smoking history were
similar between the two groups. The patients with hypo-
chloremia were older than those without (69.57±7.07
years vs 68.24±6.22 years, p=0.042). Second, the mean
LVEF was less than 35% in both groups and lower in the
hypochloremic group, in which the patients had higher
values of serum creatinine on admission (Table 1). Third,
the prevalence of in-hospital death (12.9% vs 3.2%,
p<0.001) and long-term death (65.3% vs 40.0%, p<0.001)
was significantly higher in the hypochloremic patients.

Univariate logistic regression analysis showed that
admission serum chloride concentrations were inde-
pendently and inversely associated with in-hospital
mortality (OR 0.887, 95% CI 0.843 to 0.930, p<0.001).
After adjusting for age, serum calcium, serum sodium,
LVEF, lg NT-proBNP and use of diuretics, serum chloride
levels remained significantly related to in-hospital death
(OR 0.943, 95% CI 0.892 to 0.998, p=0.042).

ROC curve analyses showed that serum chloride had
excellent predictive ability for in-hospital and long-term
death (area under the curve (AUC) = 0.690, p<0.001, and
AUC = 0.710, p<0.001, respectively) (Figure 1). A total of
461 all-cause deaths (305 men and 156 women) were
recorded during the follow-up period. Kaplan-Meier
survival estimates showed that the patients with hypo-
chloremia had a lower cumulative survival rate (log-rank
$\chi^2$ = 56.69, p<0.001) (Figure 2).

The multivariate Cox proportional hazard analysis
showed that serum chloride remained a significant
predictor for long-term mortality after adjusting for age,
serum calcium, serum sodium, LVEF, lg NT-proBNP
and use of diuretics (HR 0.934, 95% CI 0.913 to 0.954,
p<0.001). Meanwhile, hypochloremia was a risk factor
for all-cause death in elderly patients with NIDCM (HR
1.584, 95% CI 1.181 to 2.124, p=0.002) (Table 2).

DISCUSSION
NIDCM has a high incidence in populations and often
leads to HF and heart transplantation,2 3 accompanied
by poor prognosis and high 3-year treated mortality.9
Older age was independently associated with impaired
survival,15 so it is important to identify high-risk older
patients early to improve their survival rate by choosing
the appropriate treatment. However, there are limited
studies in elderly patients with NIDCM. Studies in recent
years have reported that hypochloremia is frequently
present in different HF populations and that it is asso-
ciated with a poor diuretic response and a higher risk of
death,16–18 which suggests that chloride concentrations
may be related to the prognosis of NIDCM.

To explore the relationship mentioned previously, we
selected a relatively large Chinese cohort to study the
prognostic role of serum chloride in elderly patients with NIDCM. The results showed that serum chloride concentrations on admission had a potential ability to predict in-hospital and long-term death, and hypochloremia was associated with lower survival, which indirectly reflected the pathological role of serum chloride in the progression of DCM, illuminating its prognostic role.

NIDCM is a heterogeneous heart muscle disease involving changes in the structure and composition of cardiomyocytes that lead to myocardial remodelling and severe impaired cardiac function. Plasma levels of NT-proBNP and LVEF have been proven to be powerful prognostic biomarkers of cardiac disease; after adjusting for them, serum chloride remained independently associated with clinical outcome in this study. In addition, patients with DCM often receive diuretic treatment, which may promote the depletion of chloride and sodium. Serum calcium is recognised as an important electrolyte for maintaining cardiac function. Our study showed that serum chloride concentrations were still independently associated with in-hospital and long-term death after multivariable adjustment for potential confounders, including serum sodium and calcium levels and the use of diuretics, while serum sodium levels were no longer related to prognosis. These findings suggest that chloride provided stronger prognostic power than sodium, which is consistent with previous studies reporting that serum chloride but not serum sodium was a strong predictor of mortality in patients with HF. When considering electrolyte disturbances in cardiovascular disease, people have often tended to focus on hyponatremia, and the effect of serum chloride is largely ignored. This real-world observational study verified that chloride plays a key role in the progression of cardiovascular disease in a relatively large cohort of NIDCM, making up for the deficiency of randomised controlled trials.

### Table 1 Baseline demographics and clinical characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hypochloremia (n=101)</th>
<th>Non-hypochloremia (n=987)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.57±7.07</td>
<td>68.24±6.22</td>
<td>0.042</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>67 (66.3)</td>
<td>644 (65.2)</td>
<td>0.827</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>33 (32.7)</td>
<td>256 (25.9)</td>
<td>0.144</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25 (24.8)</td>
<td>328 (33.2)</td>
<td>0.083</td>
</tr>
<tr>
<td>Diabetes</td>
<td>24 (23.8)</td>
<td>237 (24.0)</td>
<td>0.955</td>
</tr>
<tr>
<td>Parameters on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>132.49±5.33</td>
<td>138.6±5.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>8.71±0.56</td>
<td>8.98±0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC count (10^9/L)</td>
<td>7.13±2.33</td>
<td>7.54±2.85</td>
<td>0.163</td>
</tr>
<tr>
<td>Neutrophil count (10^9/L)</td>
<td>4.68±2.1</td>
<td>5.06±2.62</td>
<td>0.161</td>
</tr>
<tr>
<td>Lymphocyte count (10^9/L)</td>
<td>1.59±0.64</td>
<td>1.65±1.15</td>
<td>0.603</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>131.1±19.5</td>
<td>131.27±18.69</td>
<td>0.932</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>11.5±8.84</td>
<td>8.57±6.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CREA (µmol/L)</td>
<td>146.14±103.25</td>
<td>108.9±69.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric (µmol/L)</td>
<td>554.9±194.06</td>
<td>497.94±153.52</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholinesterase (U/L)</td>
<td>5894.65±5823.80</td>
<td>6785.56±2145.45</td>
<td>0.003</td>
</tr>
<tr>
<td>TBIL (µmol/L)</td>
<td>36.7±29.34</td>
<td>21.11±21.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBIL (µmol/L)</td>
<td>14.24±15.33</td>
<td>6.21±9.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiographic features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>43.92±9.40</td>
<td>43.8±8.02</td>
<td>0.911</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>65.87±9.72</td>
<td>65.56±9.12</td>
<td>0.784</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>29.0±8.0</td>
<td>33.0±11.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CREA, creatinine; DBIL, direct bilirubin; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricle ejection fraction; NIDCM, non-ischaemic dilated cardiomyopathy; TBIL, total bilirubin; WBC, white blood cell.
These results could be explained by the regulatory role of chlorine in neurohormone activation. Patients with NIDCM are frequently admitted because of HF symptoms, including chronic HF and acute decompensated HF, whereas those enrolled in this study presented with a mean LVEF lower than 35%, which suggests a higher risk of SCD. When the cardiac ejection fraction decreases, compensatory homeostatic responses to the decrease in cardiac output are activated, such as the activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS); however, chronic activation of these neurohormonal systems will exert deleterious effects on the heart. It was reported that hypochloremia is related to higher renin secretion and then improves RAAS activity, resulting in worsening HF. Meanwhile, the stimulation of angiotensin II and aldosterone will also promote the excretion of chloride, which is involved in the development of hypochloremia. This means that the relationship between hypochloremia and RAAS activity is complex and closely related to HF pathophysiology.

In chronic HF, hypochloremia may be dilutional in nature and may result from an increased release of arginine vasopressin that promotes free-water reabsorption in the renal collecting ducts, and increased angiotensin II activation can stimulate aldosterone secretion, resulting in fluid retention. On the other hand, hypochloremia could also be depletional because of diuretic-induced salt wasting, especially when chloride is lower relative to sodium. Loop diuretics primarily inhibit the sodium–potassium–chloride cotransporter (NKCC) to reduce sodium and chloride reabsorption, which may lead to excessive chloride wasting. The asymmetrical reduction of sodium and chloride in plasma compartments may be due to chloride being excreted in the urine while bicarbonate is being retained to maintain electroneutrality. In addition, NKCC has a role in maintaining myocardial volume and pH levels; if acid-base imbalance occurs, myocardial contractility will be impaired.

The use of loop and thiazide diuretics can effectively reduce the plasma volume by depleting serum chloride; however, these diuretics may induce hypochloremia that could lead to diuretic resistance. Previous studies indicated that acetazolamide, sodium glucose cotransporter 2 inhibitors and vasopressin receptor antagonists have the potential ability to increase serum chloride concentration while decreasing plasma volume, but further randomised controlled trials are required to verify the efficiency of these therapies. When hypochloremia is observed in patients with DCM, clinicians should choose diuretics carefully. Hypertonic saline and lysine chloride (an orally administered organic chloride salt) may directly enhance serum chloride levels, but their pharmacological impact is not clear, whereas correction of electrolyte imbalance can improve hemodynamics, myocardial contractility and prognosis of patients.

The present study highlights that the analysis of serum chloride concentrations remains favourable to refine outcomes of patients and provides new insights into the clinical strategies of DCM, such as the correction of chloride disturbance. Meanwhile, it provides the information needed to further study the mechanism of hypochloremia and emphasises the requirement to consider it when predicting the mortality of patients with DCM.

This is a retrospective study, and some limitations need to be clarified. In our study, serum chloride concentrations were measured at specific time points, but the influence of time-related changes cannot be ignored. The impact of changes in chloride levels on the prognosis is difficult to estimate. These patients are often admitted to the hospital due to worsening HF. It is difficult to know from the medical records whether hypochloremia was corrected during hospitalisation. Future studies should evaluate whether the strict monitoring and correction of hypochloremia have a beneficial effect on prognosis.
Table 2  Multivariate Cox proportional hazard regression models for long-term mortality

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum chloride, mmol/L*</td>
<td>0.934</td>
<td>0.913 to 0.954</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.038</td>
<td>1.022 to 1.055</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium, mg/dL</td>
<td>0.840</td>
<td>0.694 to 1.017</td>
<td>0.074</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>1.018</td>
<td>0.993 to 1.045</td>
<td>0.156</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.984</td>
<td>0.973 to 0.996</td>
<td>0.010</td>
</tr>
<tr>
<td>Ig NT-proBNP</td>
<td>1.601</td>
<td>1.306 to 1.963</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of diuretics</td>
<td>1.268</td>
<td>0.828 to 1.941</td>
<td>0.275</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypochloremia*</td>
<td>1.584</td>
<td>1.181 to 2.124</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.038</td>
<td>1.022 to 1.054</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium, mg/dL</td>
<td>0.848</td>
<td>0.704 to 1.023</td>
<td>0.085</td>
</tr>
<tr>
<td>Serum sodium, mmol/L</td>
<td>0.997</td>
<td>0.986 to 1.009</td>
<td>0.652</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.981</td>
<td>0.970 to 0.993</td>
<td>0.002</td>
</tr>
<tr>
<td>Ig NT-proBNP</td>
<td>1.645</td>
<td>1.338 to 2.023</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of diuretics</td>
<td>1.295</td>
<td>0.845 to 1.984</td>
<td>0.235</td>
</tr>
</tbody>
</table>

*Adjusted for age, serum calcium, serum sodium, LVEF, Ig NT-proBNP and use of diuretics as time-varying covariates.
LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONCLUSIONS
Serum chloride concentration was a prognostic indicator in elderly patients with NIDCM, and hypochloremia was significantly associated with both in-hospital and long-term poor outcomes, which may be related to haemodynamic abnormalities and activation of the neurohormonal system. The present study showed that analysis of serum chloride concentrations remains favourable in determining the outcomes of patients, but large prospective randomised clinical trials are still required to evaluate the negative effects of hypochloremia and the clinical benefits of serum chloride-enhancing therapies in patients with DCM.

REFERENCES


