Hypochloreaemia and 30 day readmission rate in patients with acute decompensated heart failure

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Abstract

Aims Despite recent advances in guideline-directed therapy, rehospitalization rates for acute decompensated heart failure (ADHF) remain high. Recently published studies demonstrated the emerging role of hypochloreaemia as a predictor of poor outcomes in patients with ADHF. This study sought to determine the correlation between low serum chloride and 30 day hospital readmission in patients with ADHF.

Methods and results We retrospectively reviewed electronic medical records of 1504 patients who were admitted to one 700 bed US tertiary care centre with the diagnosis of ADHF between June 2013 and December 2014. Of the 1504 reviewed records, 1241 were selected for further analysis. Hypochloreaemia (either on admission or at discharge) was identified in 289 patients (23.3%) and was associated with significantly higher 30 day hospital readmission rate or death (42.2% vs. 33.7%, P = 0.008). This association persisted in multivariate analysis when controlling for serum sodium, weight loss, diuretic dose, adjunct thiazide use, serum blood urea nitrogen, and BNP levels (OR: 1.35, 95% CI: 1.02–1.77, P = 0.033); however, the predictive value of the overall model was low (Nagelkerke $R^2 = 0.040$). Hypochloreaemia was also found to be associated with increased 12 month mortality in our cohort (31.4% vs. 20.2%, P = 0.015) that correlates with the results of previously published studies.

Conclusions Low serum chloride measured in patients admitted for ADHF is independently but weakly associated with increased 30 day readmission rate and demonstrated low predictive value as a potential biomarker in this cohort.

Keywords Acute decompensated heart failure; Chloride; Readmission

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Background

Despite advances in guideline-directed therapy, rehospitalization rates for acute decompensated heart failure (ADHF) remain high.1,2 Readmission costs are estimated at $12 billion annually to the US healthcare system.3 Early identification of patients at highest risk for heart failure (HF) readmission may allow for addition of more intensive resources to potentially reduce readmission rates.4 Recently published studies demonstrated the emerging role of low serum chloride as an independent predictor of diuretic resistance and poor outcomes in patients with ADHF.5–7 However, the prognostic value of hypochloreaemia specifically for hospital readmissions remains unclear.

Aims

We aimed to study the correlation between low serum chloride and 30 day hospital readmission in patients with ADHF.

Methods

Study design

We retrospectively reviewed sequential electronic medical records of 1504 patients who were admitted to one 700 bed US tertiary care centre with the primary diagnosis of ADHF.
discharge. Blood urea nitrogen (BUN), GFR, and BNP on admission and of diuretics, left ventricular ejection fraction (LVEF), and se-

New York Heart Association class, weight on admission and percentages. Univariate analysis was conducted using the
categorical variables were presented as frequencies and per-
 Continuous variables were presented as mean ± SD, and cat-

Statistical analysis

Collected data included demographic information, length of stay, data on 30 day hospital readmission, 12 month survival, New York Heart Association class, weight on admission and discharge, information on medical regimen including doses of diuretics, left ventricular ejection fraction (LVEF), and serum values of sodium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN), GFR, and BNP on admission and discharge.

Clinical data collection

The study was approved by the Tower Health Institutional Review Board (Protocol number IRB 013E-17). Because of retrospective nature of the study, no informed consent from the subjects was required.

Results

Of the 1504 reviewed electronic medical records, 1241 were selected for further analysis. Detailed patient characteristics are outlined in Table 1. The mean age in the study cohort was 76.5 ± 13.0 years and 52.3% (649) were male. The mean LVEF was 48.0 ± 17.5%. Ischaemic cardiomyopathy accounted for 64.9% of the causes of HF, and 50.6% were diabetic. Of the 994 patients with records available at 1 year, 12 month mortality was 21.1% [247 (19.9%) were lost to follow-up at 1 year]. Mean admission chloride was 102.4 ± 5.1 mEq/L, with 120 patients (9.7%) having hypochloraemia on admission, 239 (19.3%) on discharge, 70 (5.6%) on both admission and discharge, and 289 (23.3%) either on admission or discharge. This latter group was included into further univariate analysis and compared with the group of patients with no hypochloraemia. Low chloride group had fewer African–American patients compared to nonhypochloraemia group (3.8% vs. 6.2%, P < 0.001), had higher LVEF (48.9 ± 17.7% vs. 47.7 ± 17.4%, P = 0.002), lower admission sodium (136.0 ± 4.8 vs. 137.9 ± 3.3 mEq/L, P < 0.001), higher bicarbonate (29.9 ± 4.6 vs. 26.0 ± 3.6 mEq/L, P < 0.001), and BUN (35.4 ± 25.7 vs. 31.4 ± 20.6 mg/dL, P = 0.016). Groups did not differ in age, sex, admission heart rate, blood pressure, New York Heart Association class, rates of ischaemic cardiomyopathy, coronary revascularization, diabetes, serum creatinine, GFR, and BNP.

Patients with hypochloraemia had more significant weight loss during hospitalization (3.9 ± 6.0 vs. 3.4 ± 4.5 kg, P < 0.001), higher maximum 24 h IV loop diuretic dose (224.7 ± 173.6 vs. 165.8 ± 133.4 mg, P < 0.001), more frequent in-hospital adjunct thiazide diuretic use (26% vs. 6.3%, P < 0.001), lower discharge sodium (134.6 ± 3.7 vs. 137.6 ± 2.9 mEq/L, P < 0.001), higher discharge bicarbonate (32.4 ± 4.7 vs. 28.6 ± 3.5 mEq/L, P < 0.001), and BUN (41.2 ± 27.2 vs. 35.8 ± 20.6 mg/dL, P = 0.002). Hypochloraemia was associated with significantly higher 30 day hospital readmission rate or death (42.2% vs. 33.7%, P = 0.008), as well as with higher 12 month mortality (31.4% vs. 20.2%, P = 0.015). A multivari-able logistic regression model was built using continuous variables that showed statistical significance in univariate analysis in addition to serum BNP and systolic blood pressure, which have been shown to be significant in prior studies. Based on multivariate analysis, hypochloraemia was associated with 30 day hospital readmission rate (OR: 1.35, 95% CI: 1.02–1.77, P = 0.033). This association was independent intervals, the initial model prediction as well as the final model prediction.

Statistical analysis was performed using SPSS software version 25 (IBM SPSS Statistics for Windows; IBM Corporation, Armonk, NY).
Table 1 Clinical characteristics based on chloride value either on admission or discharge.

| Variable                       | All Patients (n = 1241) | Hypochloraemia | P value |
|--------------------------------|-------------------------|----------------|---------|
| Age (years)                    | 76.5 ± 13.0             | 76.4 ± 13.1    | 76.6 ± 12.7 | 0.861 |
| Male, % (n)                    | 52.3 (649)              | 52.6 (501)     | 51.2 (148) | 0.673 |
| Black race, % (n)              | 5.6 (70)                | 6.2 (59)       | 3.8 (11)  | <0.001 |
| LVEF, %                        | 48.0 ± 17.5             | 47.7 ± 17.4    | 48.9 ± 17.7 | 0.002 |
| SBP (mmHg)                     | 150.1 ± 33.3            | 151.7 ± 33.1   | 144.7 ± 33.7 | 0.260 |
| DBP (mmHg)                     | 80.2 ± 17.7             | 80.5 ± 17.3    | 79.1 ± 18.9 | 0.139 |
| HR (bpm)                       | 83.1 ± 19.4             | 82.7 ± 19.4    | 84.6 ± 19.6 | 0.412 |
| Hypertension, % (n)            | 93.5 (1160)             | 93.3 (888)     | 94.1 (272) | 0.612 |
| Ischaemic cardiomyopathy, % (n)| 64.9 (805)              | 64.6 (615)     | 65.7 (190) | 0.721 |
| NYHA class III/IV, % (n)       | 78.4 (940)              | 77.9 (718)     | 79.9 (222) | 0.500 |
| PCI, % (n)                     | 27.9 (346)              | 28.2 (268)     | 27.0 (78)  | 0.700 |
| CABG, % (n)                    | 26.4 (328)              | 27.0 (257)     | 24.6 (71)  | 0.412 |
| ICD therapy, % (n)             | 11.8 (146)              | 12.1 (115)     | 10.0 (29)  | 0.342 |
| Diabetes, % (n)                | 50.6 (628)              | 49.4 (470)     | 54.7 (158) | 0.114 |
| Sodium (mEq/L)                 | 137.3 ± 3.9             | 137.9 ± 3.3    | 136.0 ± 4.8 | <0.001 |
| Bicarbonate (mEq/L)            | 26.7 ± 4.1              | 26.0 ± 3.6     | 29.9 ± 4.6  | <0.001 |
| BUN (mg/dL)                    | 29.5 ± 4.1              | 28.6 ± 3.5     | 24.7 ± 3.7  | <0.001 |
| Creatinine (mg/dL)             | 29.5 ± 4.1              | 28.6 ± 3.5     | 24.7 ± 3.7  | <0.001 |
| Chloride (mg/dL)               | 102.4 ± 5.1             | 103.9 ± 4.0    | 97.2 ± 5.1  | <0.001 |
| BNP (pg/mL)                    | 1267.4 ± 1121.4         | 1278.0 ± 1131.4| 1232.7 ± 1089.2 | 0.548 |
| Maximum 24 h IV loop diuretic dose (mg) | 115.5 ± 145.8 | 165.8 ± 133.4 | 173.6 ± 127.6 | <0.001 |
| In-hospital thiazide diuretic use, % (n) | 10.9 (135) | 6.3 (60) | 26.0 (75) | <0.001 |
| Weight loss during hospitalization (kg) | 3.5 ± 6.1 | 3.4 ± 4.5 | 3.9 ± 9.6 | <0.001 |
| Length of stay (days)          | 6.4 ± 4.5               | 6.0 ± 4.3      | 7.6 ± 4.8  | 0.315 |
| Discharge labs                  |                        |                |         |
| Sodium (mEq/L)                 | 136.9 ± 3.3             | 137.6 ± 2.9    | 134.6 ± 3.7 | <0.001 |
| Bicarbonate (mEq/L)            | 29.5 ± 4.1              | 28.6 ± 3.5     | 32.4 ± 4.7  | <0.001 |
| BUN (mg/dL)                    | 37.1 ± 22.4             | 35.8 ± 20.6    | 41.2 ± 27.2 | 0.002 |
| Creatinine (mg/dL)             | 1.8 ± 1.4               | 1.8 ± 1.4      | 1.8 ± 1.2  | 0.998 |
| Chloride (mg/dL)               | 99.4 ± 4.7              | 101.2 ± 3.4    | 93.5 ± 3.6  | <0.001 |
| Thirty day hospital readmission or death, % (n) | 35.7 (443) | 33.7 (321) | 42.2 (122) | 0.008 |
| Twelve month mortality, % (n)a | 21.1 (210)              | 20.2 (183)     | 31.4 (27)  | 0.015 |

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
aBased on 994 records available at 1 year; 247 subjects were lost to follow-up.

of serum sodium levels. Serum sodium did not show significant association with readmission in the regression model. However, despite the presence of this association, chloride values demonstrated a very low predictive value (Naglkerke $R^2 = 0.040$).

**Discussion**

In this study, we identified that low serum chloride was independently associated with increased 30 day hospital readmission rate, even after multivariable adjustment for other variables such as race, systolic blood pressure, LVEF, serum sodium, BNP, bicarbonate, BUN, weight change during hospitalization, maximum 24 h IV loop diuretic dose, and inpatient thiazide diuretic use percentage. However, serum chloride alone, although statistically associated with readmission, was found to have a low predictive value, predicting only 4% of readmission outcomes, which may limit its clinical utility if used in isolation. Our low chloride groups differed from admission to discharge, with only 5.6% identified as hypochloraemic throughout admission, similar to a study from Ter Maaten et al., suggesting that this finding may be an effect of treatment rather than a stable, identifiable trait. Finally, hypochloraemia was associated with increased 12 month mortality, which correlates with the results of previously published studies highlighting the role of hypochloraemia in adverse outcomes in patients with ADHF.

Despite recent evolution in understanding of role of chloride homeostasis in HF, mechanisms of association between chloride and adverse HF outcomes remain unclear. It is still uncertain if chloride plays an independent role in pathophysiology of HF, or its impaired homeostasis is just a downstream effect of neurohormonal activation cascade, worsened renal function, associated acid-base disturbances, or pharmacologic interventions including more aggressive diuretic use.

There is a growing body of evidence suggesting important role of chloride in patients with chronic HF, subsets of HF with
preserved and reduced ejection fraction, acute myocardial infarction, and systemic and pulmonary hypertension.\textsuperscript{10–12}

At the same time, the prognostic role of chloride as a biomarker in HF remains in question.\textsuperscript{13} Meanwhile, trials to determine if interventions in serum chloride levels will have a positive effect on HF treatment are currently underway (NCT03446651).

**Study limitations**

This was a retrospective single centre data analysis, and the findings in our patient population may be unique to this centre, its care patterns, or population. Our lost-to-follow-up group (19.9% at 1 year) could have preferentially missed number of deaths in either arm, ultimately affecting the ability of chloride to predict 1 year mortality.

**Conclusions**

Low serum chloride measured in patients admitted for ADHF is independently associated with increased 30 day readmission rate. At the same time, based on multivariate analysis, this association seems to be weak with chloride demonstrating low predictive value as a potential biomarker. A dedicated clinical trial meeting novel biomarker study quality requirements is needed to clarify potential prognostic role of this electrolyte in HF, but inclusion of chloride in future multimarker predictive scoring models should be considered.

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