ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 903–907
Published online 14 April 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12587

SHORT COMMUNICATION

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

Roman Marchenko*, Adam Sigal, Thomas E. Wasser, Jessica Reyer, Jared Green, Christopher Mercogliano, Muhammad Sohail Khan and Anthony A. Donato

Reading Hospital, Tower Health Medical Group, West, Reading, PA, USA

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 hypochloraemia 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. Hypochloraemia (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 (Naglkerke $R^2 = 0.040$). Hypochloraemia 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

Received: 14 June 2019; Revised: 13 November 2019; Accepted: 22 November 2019
**Correspondence to:*
Roman Marchenko, Reading Hospital, Tower Health Medical Group, 420 S. Fifth Ave, West Reading, PA 19611, USA.
Email: rmarchen@yahoo.com

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 hypochloraemia 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

requiring intravenous diuretics between June 2013 and December 2014. Patients older than 18 years with at least 30 days of available medical records following admission were enrolled. Patients were excluded if they had ongoing left ventricular mechanical support, history of heart transplantation, severe comorbidities including acute severe hepatic impairment, severe pulmonary disease, severe stenotic valvular heart disease, acute myocarditis, constrictive pericarditis, cardiac tamponade, acute coronary syndrome, aortic dissection, contrast-induced nephropathy, or other acute kidney injury of renal or postrenal aetiology, sepsis, noncardiogenic pulmonary oedema, acute bleeding requiring blood transfusion.

Hypochloraemia was defined as the level of electrolyte greater than two standard deviations below the mean in the normal distribution ($<$96 mmol/L).[8]

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.

Clinical data collection

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.

Statistical analysis

Continuous variables were presented as mean ± SD, and categorical variables were presented as frequencies and percentages. Univariate analysis was conducted using the dichotomized serum chloride variable ($<$96 mEq/L vs. $\geq$96 mEq/L) to divide patients into hypochloraemia and nonhypochloraemia groups. Chi-square analysis was performed on categorical variables and group *t*-tests was conducted on continuous variables. A global *P* value of 0.05 was considered statistically significant for each test. Because of the exploratory nature of this data analysis, no corrections were applied to the data for multiple comparisons.

Logistic regression analysis was performed using those variables that reached statistical significance in univariate testing to create a predictive model of low serum chloride. The entry method for the logistic regression was backwards elimination using the Wald statistic. The criteria for elimination were the default pin and pout of 0.05 and 0.10, respectively. The outcomes reported for this analysis included the beta coefficient for each variable, the odds ratio along with 95% confidence 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).

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 ± 9.6 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 multivariable 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.[5] 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

Table 1 Clinical characteristics based on chloride value either on admission or discharge.

Variable	All Patients (n = 1241)	Hypochloraemia		P value
		No (n = 952)	Yes (n = 289)	
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)	32.3 ± 21.9	31.4 ± 20.6	35.4 ± 25.7	0.016
Creatinine (mg/dL)	1.8 ± 1.7	1.8 ± 1.6	1.9 ± 1.9	0.464
Chloride (mg/dL)	102.4 ± 5.1	103.9 ± 4.0	97.2 ± 5.1	<0.001
eGFR (Cockcroft-Gault) (mL/min)	52.6 ± 34.4	52.7 ± 34.1	52.1 ± 35.2	0.805
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)	179.5 ± 145.8	165.8 ± 133.4	224.7 ± 173.6	<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.
[a]Based 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.,[5] 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.[5,7]

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.[7,9]

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.[10–12]

At the same time, the prognostic role of chloride as a biomarker in HF remains in question.[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.

Conflict of interest

Drs Roman Marchenko, Adam Sigal, Thomas E. Wasser, Jessica Reyer, Jared Green, Christopher Mercogliano, Muhammad Sohail Khan, and Anthony A. Donato have no conflict of interests or financial ties to disclose.

Compliance with ethical standards

The study was conducted in accordance with the international, national, and institutional ethical standards and was approved by local institutional review board. Informed consent from included subjects was waived based on the following criteria: (i) the study could not practically be carried out without the waiver of informed consent (some subjects not alive or had moved out of the area by the time of study conduction, not possible to contact all of the subjects as the validity of the study depended on inclusion of all subjects); (ii) the waiver or alteration of informed consent did not adversely affect the subject rights and welfare (no direct patient contact or interventions).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Tower Health Institutional Review Board; protocol number IRB 013E-17) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

References

1. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA* 2013; **309**: 355–363.
2. Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, Bernheim SM, Wang Y, Bradley EH, Han LF, Normand SL. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. *JAMA* 2013; **309**: 587–593.
3. Lee WC, Chavez YE, Baker T, Luce BR. Economic burden of heart failure: a summary of recent literature. *Heart Lung* 2004; **33**: 362–371.
4. Naylor MD, Brooten DA, Campbell RL, Maislin G, Mccauley KM, Schwartz JS. Transitional care of older adults hospitalized with heart failure: a randomized, controlled trial. *J Am Geriatr Soc* 2004; **52**: 675–684.
5. Ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, Cleland JG, Bloomfield DM, Hillege HL, van Veldhuisen DJ, Voors AA, Testani JM. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail* 2016; **9**. e003109
6. Grodin JL, Sun JL, Anstrom KJ, Chen HH, Starling RC, Testani JM, Tang WH. Implications of serum chloride homeostasis in acute heart failure (from ROSE-AHF). *Am J Cardiol* 2017; **119**: 78–83.
7. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, Starling RC, Testani JM, Tang WH. Prognostic role of serum chloride levels in acute decompensated heart failure. *J Am Coll Cardiol* 2015; **66**: 659–666.
8. Yunos NM, Bellomo R, Story D, Kellum J. Bench-to-bedside review: chloride in critical illness. *Crit Care.* 2010; **14**: 226.
9. Tang WH, Mullens W. Cardiorenal syndrome in decompensated heart failure. *Heart* 2010; **96**: 255–260.
10. Ferreira JP, Girerd N, Duarte K, Coiro S, McMurray JJ, Dargie HJ, Pitt B, Dickstein K, Testani JM, Zannad F, Rossignol P. Serum chloride and sodium interplay in patients with acute myocardial infarction and heart failure with reduced ejection fraction: an analysis from the high-risk myocardial infarction database initiative. *Circ Heart Fail* 2017; **10**. e003500
11. McCallum L, Jeemon P, Hastie CE, Patel RK, Williamson C, Redzuan AM, Dawson J, Sloan W, Muir S, Morrison D, McInnes GT, Freel EM, Walters M, Dominiczak

AF, Sattar N, Padmanabhan S. Serum chloride is an independent predictor of mortality in hypertensive patients. *Hypertension* 2013; **62**: 836–843.

12. Naal T, Abuhalimeh B, Khirfan G, Dweik RA, Tang WHW, Tonelli AR. Serum chloride levels track with survival in patients with pulmonary arterial hypertension. *Chest* 2018; **154**: 541–549.
13. O'connor CM, Ahmad T. The role of sodium and chloride in heart failure: does it take two to tango? *J Am Coll Cardiol* 2015; **66**: 667–669.