CORRELATION OF SERUM CHLORIDE LEVELS WITH 30 DAY MORTALITY IN HEART FAILURE PATIENTS

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ABSTRACT

BACKGROUND

Heart failure is commonly associated with electrolyte imbalances. Hyponatraemia has established prognostic role in heart failure, but association of hypochloraemia is still lacking. We wanted to study the impact of admission serum chloride levels in relation to serum sodium levels in 30-day outcomes after hospitalization for acute decompensated heart failure (ADHF).

METHODS

Total of 405 consecutive patients with diagnosis of ADHF were assessed for serum sodium and serum chloride levels on admission within the period of 2.5 years, and divided into 3 tertiles based on serum chloride levels and observed for 30 day outcome. Continuous variables were compared using independent t-test while $\chi 2$ test was used for categorical variables. p-value ≤ 0.05 considered significant.

RESULTS

Mean age was found to be 62.5 yrs. Overall mortality at 30 days was 24.4% (99) and all deaths occurred in tertile 1 (serum Cl <99), suggesting strong role of hypochloraemia in mortality. Patients in tertiles 2 (99-103) and tertiles 3 (>103) exhibited 100% survival.

CONCLUSIONS

Mortality at 30 days in patients with ADHF is 24.4 percent and serum chloride is strongly and independently associated with poor survival in these patients and has a major contribution in the risk caused due to hyponatraemia.

KEYWORDS

Acute Decompensated Heart Failure, Hypochloraemia, Hyponatraemia

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BACKGROUND

Heart failure (HF) is commonly associated with electrolyte disturbances most commonly hyponatremia.[1] Up-regulation of maladaptive neurohormonal systems is the main culprit during acute decompensation of HF that decrease solute and free water delivery to the distal nephron which increases free water absorption causing dilutional dyselectrolytemia. Use of diuretics and other decongestive therapies further exacerbates the situation.

Various literature indicate that even mild hyponatraemia is a strong predictor of adverse events like decreased survival, rehospitalisation, prolonged length of stay and increasing cost of healthcare.[1-3]

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This association of hyponatraemia for poor prognosis in heart failure is independent of traditional disease severity indicators.[4-9]

Hyponatraemia is by definition usually associated with other electrolyte imbalances like hyponatraemia, hypomagnesaemia etc. and in order to maintain electro neutrality, an anion like chloride or bicarbonate must be reduced with the sodium during transport.

Previously serum chloride is considered to be passively associated anion with sodium. However renal salt sensing mechanisms are mainly governed by chloride in spite of sodium.[10-13]

A family of serine-threonine kinases (With-No-Lysine (K), WNK) found to be involved in the regulation of RAS system, sodium chloride homeostasis and the transporters upon which loop and thiazide diuretics work.[14] Chloride binds directly to the catalytic site of these kinases and phosphorylate sodium-regulatory pathways.[15,16]

Since two important pathways of heart failure that is neurohormonal activation and sodium homeostasis both directly controlled by chloride in spite of sodium, we hypothesized that serum chloride may also be an important prognostic factor.

Aim of The Study

To study the impact of admission serum chloride levels in relation to serum sodium levels in 30-day outcomes after hospitalization for ADHF.

METHODS

We identified 405 unique, consecutive patients admitted to the cardiology department at our institute between November 2015 and May 2018 with a discharge diagnosis of acute decompensated heart failure (ADHF). Framingham's criteria were used for the diagnosis of heart failure in the study.

Study Population

1. Consecutive patients admitted in coronary care unit in the department of Cardiology, Government medical college Kozhikode, with the diagnosis of ADHF.
2. Only the first admission for a patient was included in the cohort if they were subsequently readmitted.

Duration of Study

2.5 years.

Sample Size

405 patients.

Clinical, demographic, laboratory data noted on admission and documented primary and secondary diagnoses were reviewed from the documented medical record. Admission chloride was defined as the serum level of chloride on first blood draw on presentation.

Inclusion Criteria

1. All patients admitted with the diagnosis of ADHF.
2. B-type natriuretic peptide level (BNP) >100 pg/ml within 24 h of admission.
3. Only the first admission was included if the patient had multiple admission history.

Patients were excluded if loop diuretics were not used for treatment on admission. Patients were then followed after 30 days for all-cause mortality via telephonic conversation.

Definitions

Hyponatraemia ≤135 mg/dL
Hypochloraemia ≤96 mg/dL

Statistical Methods

Continuous variables expressed as mean and categorical variables as percent. (Table 3) Independent Student's t-test was used to compare continuous variables. (Table 4) The $\chi 2$ test was used to evaluate associations between categorical variables. (Table 2) Hazard ratios (HRs) and 95% confidence intervals (Cis) for all-cause mortality will be determined for various covariates. P- Values <0.05 were considered statistically significant. SPSS software used for statistical analysis.

RESULTS

Baseline Characteristics

Baseline characteristics for cohort are shown in Table 1. Mean age found to be 62.5 yrs. Most of the patients were elderly and this age group was associated with high mortality. Males and females were equally distributed and Male gender found to have significantly high mortality. Dyspnoea was the most common presenting symptom and hypertension followed by DM were the most common associated comorbidity. All patients treated with loop diuretics.

Patients were divided into three tertiles (i.e. serum chloride <99 is tertile 1, 99-103 is tertile 2 and >103 is tertile 3).

Admission chloride levels were normally distributed (i.e. 44.4% pts. belong to tertile: 1 while 28.9% and 26.7% pts. belong to tertiles: 2 and 3 respectively) with mean admission chloride being 99 (interquartile range: 85 to 110) mEq/l.

Mean serum sodium was 129.9±6.7 mEq/l (Table 2). Hyponatraemia (Na+ ≤135) present in 315(77.8%) patients. Mean LVEF was 46±12%. Admission chloride levels were directly correlated to admission sodium levels (p <0.001). Higher chloride levels were found in patients with increasing LV ejection fraction, beta-blocker and renin-angiotensin system–blocker and MRA use while lower levels were associated with history of previous CAD, N-terminal pro–B-type natriuretic peptide levels and indicators of end-organ function (haemoglobin and deranged LFT) (Table 3).

Chloride Levels and 30-Day Mortality

Overall mortality at 30 days was 24.4% (99) (Figure 1) and all deaths occurred in tertile 1, suggesting strong role of hypochloraemia in mortality. Patients in tertiles 2 and tertiles 3 exhibits 100% survival (Figure 2).

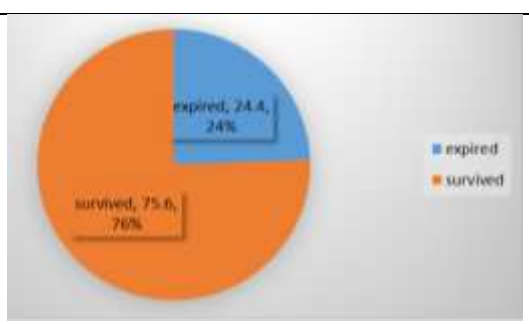

Figure 1. 30 Days Mortality

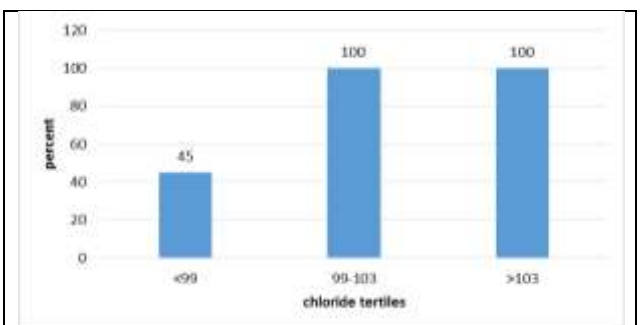

Figure 2. Survival Characteristics

Patient Characteristics	Frequency, n (%)
Mean Age (yrs.)	62.5
Age Groups (yrs.)	
0 - 3 9	9 (2.2)
4 0 - 4 9	36(8.9)
5 0 - 5 9	54 (13.3)
6 0 - 6 9	189 (46.7)
≥70	117 28.9)
Sex	
Males	198(48.9)
Females	207(51.1)
Symptoms	
Chest pain	81(20)
Palpitations	63(15.6)
Syncope	27(6.7)
Oedema	90(22.2)
Orthopnoea	207(51.1)
PND	99(24.4)
Dyspnoea	351(86.7)
Comorbidities	
HTN	225(55.6)
DM	153(37.8)
CVA	0
DLP	72(17.8)
Smoking	117(28.9)
Old CAD	135(33.3)
Drug History	
Beta blockers	351(86.7)
RAS antagonist	252(62.2)
Loop diuretics	405(100)
MRA	333(82.2)
Clinical Signs	
JVP/HJR	225(55.6)
S3	72(17.8)
Hepatomegaly	45(11.1)
Chest crepts	351(86.7)
Biochemistry	
NT-ProBNP	360(88.9)
Deranged LFT	126(31.1)
Hyponatraemia(≤135)	315(77.8)
Chloride	
<99	180(44.4)
99-103	117(28.9)
>103	108(26.7)
Outcomes (30 days Mortality)	
Expired	99(24.4)
Survived	306(75.6)

Table 1. Baseline Characteristics

	N	Minimum	Maximum	Mean	Std. Deviation
Age	405	34	80	62.578	9.67
BP Systolic	405	60	160	105.11	23.75
BP Diastolic	405	0.0	100	64.71	27.58
Heart Rate	405	40	160	98.86	22.77
Haemoglobin	405	9.5	16.8	12.269	1.6898
TLC	405	3600	19100	13331.11	3497.15
Sodium (Na)	405	116	143	129.904	6.73
Chloride (Cl)	405	85	110	99.0	5.746
Potassium (K)	405	3.2	6.0	4.180	0.6608
Creatinine	405	0.60	4.30	1.56	0.7700
LVEF	405	22.0	70	46.778	12.8254

Table 2. Descriptive Statistics

Patient Characteristics	Expired, n (%)	Survived, n (%)	p-Value	Hazard Ratio (HR)	CI (95%)
Age Groups (yrs.)					
0 - 39	9 (100)	0			
40 - 49	9 (25)	27(75)			
50 - 59	9 (16.7)	45 (83.3)	<0.001	-	-
60 - 69	63(33.3)	126 (66.7)			
≥70	9 (7.7)	108 (92.3)			
Sex					
Male	63 (31.8)	135 (68.2)	0.01	0.54	0.38-0.78
Female	36 (17.4)	171 (82.6)			
HTN	54(24)	171(76)	0.81	0.96	0.68-1.35
DM	36(23.5)	117(76.5)	0.73	0.94	0.65-1.34
DLP	18(25)	54(75)	0.90	1.02	0.66-1.6
Smoking	36(30.8)	81(69.2)	0.059	1.4	0.99-1.99
Old CAD	63(46.7)	72(53.3)	<0.001	3.5	2.45-4.98
Beta-blocker	99(28.2)	25.2(71.8)	<0.001	-	-
RAS antagonist	36(14.3)	216(85.7)	<0.001	0.3	0.24-0.49
MRA	63 (18.9)	270(81.1)	<0.001	0.37	0.27-0.52
Hyponatraemia (≤135)	99(31.4)	216(68.6)	<0.001	-	-
Chloride					
<99	99 (55)	81(45)	<0.001	-	-
99-103	0	117(100)			
>103	0	108(100)			
NT-Pro BNP (high)	99(27.5)	261(72.5)	<0.001	-	-
Deranged LFT	81(64.3)	45(35.7)	<0.001	9.9	6.25-15.86

Table 3. Comparative Analysis of Valuables Using Pearson's Chi-Square Test and Hazard Ratios

Although admission sodium levels were also inversely associated with mortality (p <0.001), admission chloride levels showed greater discrimination for mortality than admission sodium levels. Mortality risk increased with decreasing chloride levels below 99 mEq/l and did not differ at values >99 mEq/L.

DISCUSSION

In our cohort of ADHF patients with LV systolic dysfunction, we found that serum chloride levels were independently and inversely related to mortality after multivariable adjustment for other important prognostic factors like hyponatraemia. Serum chloride levels enhanced mortality prediction compared with sodium levels.

These findings were suggestive of the prognostic implications of serum chloride level in ADHF and provides stronger prognostic information than serum sodium level. The pathological role of chloride in HF is incompletely understood due to its rare inclusion in clinical trials.

Chloride accounts for approximately one third of the tonicity and two-thirds of all negative charges in the plasma.[17] Dietary sodium chloride is the main source of chloride in the body and excreted via gastric, sweat and renal route.

Mechanisms that reduce sodium levels can similarly lower chloride levels.[18] These include:

1) The pathological impairment of free water excretion resulting from increased non-osmotic release of arginine vasopressin,[19] which is typically increased in patients with symptomatic HF.[20,21]
2) The pleiotropic effects of excess angiotensin II on renal sodium and water handling and neural thirst centre activation.
3) Increased baroreceptor-mediated release of arginine vasopressin.[20]

All of these mechanisms are directly stimulated in HF.[22] As a result, lower chloride levels may be dilutional in nature. Plasma concentrations of serum sodium and serum chloride may reduce symmetrically or asymmetrically in heart failure.[23,24] This depends upon the ability of kidneys to handle these electrolytes and further modified by therapeutic agents mainly loop diuretics. Our finding that lower chloride levels were associated with higher mortality

provides important insights into interpretation of electrolytes in ADHF.

Although hyponatraemia has consistently been shown to be a strong predictor of short- and long-term morbidity and mortality in patients with HF[25,26] but the impact of chloride on the interpretation of sodium levels was not studied in these analyses. Our findings suggest that although sodium levels are important, serum chloride levels provide more robust prognostic information.

Our observations implicate the need to focus on better understanding of chloride homeostasis and considering it as a therapeutic target specifically in patients with ADHF with excessive use of loop diuretics that leads to inevitable chloride loss.

Study Limitations

The study mainly includes ADHF patients with LV systolic dysfunction with limited patients with heart failure with preserved ejection fraction. So, results of the study cannot be imposed on to this group of patients.

The impact of chloride levels on HF re-hospitalisations could not be determined. There was only a minority of patients with serum chloride levels >107 mEq/l and this analysis was underpowered to determine increased risk caused by hypochloraemia.

CONCLUSIONS

All-cause mortality at 30 days in patients with ADHF is 24.4 percent. Serum chloride is strongly and independently associated with worsened survival in these patients and has a major contribution in the risk associated with hyponatraemia. These findings suggest the role of chloride in long-term prognostication for ADHF. Because of the central role of chloride in heart failure in various regulatory pathways, it may be used as a therapeutic target.

REFERENCES

[1] Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. World J Cardiol 2013;5(9):317-328.

[2] Hauptman PJ. Clinical challenge of hyponatremia in heart failure. J Hosp Med 2012;7 Suppl 4:S6-10.

[3] Rusinaru D, Tribouilloy C, Berry C, et al. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis: Meta-Analysis Global Group in Chronic heart failure (MAGGIC). Eur J Heart Fail 2012;14(10):1139-1146.

[4] Goldsmith SR. Current treatments and novel pharmacologic treatments for hyponatremia in congestive heart failure. Am J Cardiol 2005;95(9A):14B-23B.

[5] De Luca L, Klein L, Udelson JE, et al. Hyponatremia in patients with heart failure. Am J Cardiol 2005;96(12A):19L-23L.

[6] Adrogue HJ. Consequences of inadequate management of hyponatremia. Am J Nephrol 2005;25(3):240-249.

[7] Brandimarte F, Fedele F, De Luca L, et al. Hyponatremia in acute heart failure syndromes: a potential therapeutic target. Curr Heart Fail Rep 2007;4(4):207-213.

[8] Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. Am J Kidney Dis 2013;62(1):139-149.

[9] Schrier RW, Sharma S, Shchekochikhin D. Hyponatraemia: more than just a marker of disease severity? Nat Rev Nephrol 2013;9(3):37-50.

[10] Wesson DE. Glomerular filtration effects of acute volume expansion: importance of chloride. Kidney Int 1987;32(2):238-245.

[11] Briggs JP, Schnermann JB. Whys and wherefores of juxtaglomerular apparatus function. Kidney Int 1996;49(6):1724-1726.

[12] Briggs J. The macula densa sensing mechanism for tubule-glomerular feedback. Fed Proc 1981;40(1):99-103.

[13] Kotchen TA, Welch WJ, Lorenz JN, et al. Renal tubular chloride and renin release. J Lab Clin Med 1987;110(5):533-540.

[14] Subramanya AR, Yang CL, McCormick JA, et al. WNK kinases regulate sodium chloride and potassium transport by the aldosterone-sensitive distal nephron. Kidney Int 2006;70(4):630-634.

[15] Piala AT, Moon TM, Akella R, et al. Chloride sensing by WNK1 involves inhibition of auto phosphorylation. Sci Signal 2014;7(324):ra41.

[16] Ponce-Coria J, San-Cristobal P, Kahle KT, et al. Regulation of NKCC2 by a chloride-sensing mechanism involving the WNK3 and SPAK kinases. Proc Natl Acad Sci USA 2008;105(24):8458-8463.

[17] Yunos NM, Bellomo R, Story D, et al. Bench-to-bedside review: chloride in critical illness. Crit Care 2010;14(4):226.

[18] Galla JH, Kirchner KA, Kotchen TA, et al. Effect of hypochloremia on loop segment chloride and solute reabsorption in the rat during volume expansion. Kidney Int 1981;20(5):569-574.

[19] Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342(21):1581-1589.

[20] Goldsmith SR, Francis GS, Cowley AW, et al. Increased plasma arginine vasopressin levels in patients with congestive heart failure. J Am Coll Cardiol 1983;1(6):1385-1390.

[21] Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A sub-study of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82(5):1724-1729.

[22] Tang WH, Mullens W. Cardiorenal syndrome in decompensated heart failure. Heart 2010;96(4):255-260.

[23] Friedberg CK. Electrolyte and fluid disturbances in congestive heart failure. N Engl J Med 1951;245(21):812-821.

[24] Friedberg CK. Electrolyte and fluid disturbances in congestive heart failure (concluded). N Engl J Med 1951;245(22):852-859.
[25] Konishi M, Haraguchi G, Ohigashi H, et al. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. J Card Fail 2012;18(8):620-625.
[26] Shchekochikhin DY, Schrier RW, Lindenfeld J, et al. Outcome differences in community- versus hospital-acquired hyponatremia in patients with a diagnosis of heart failure. Circ Heart Fail 2013;6(3):379-386.