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**Authors**

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# Prognostic Role of Serum Chloride Levels in Acute Decompensated Heart Failure

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**H**ear failure (HF) is often complicated by electrolyte abnormalities. As ventricular dysfunction progresses to symptomatic HF, up-regulation of maladaptive neurohormonal systems may limit solute and free water delivery to the distal nephron, increasing free water absorption and potentially reducing serum sodium and chloride levels (1,2). These electrolyte perturbations may be exacerbated through the use of decongestive therapies in acute and chronic HF (e.g., loop and thiazide diuretics)

(3-5). The finding of hyponatremia in the patient with HF is a well-established, strong predictor of short- and long-term morbidity and mortality irrespective of left ventricular (LV) systolic function (6-13).

However, the impact of hypochloremia in HF is less well understood despite its broad availability in routinely used blood chemistry panels and its common attribution to contraction alkalosis during

## ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure

CI = confidence interval

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LV = left ventricular

excessive decongestion therapy. Furthermore, lower serum chloride levels relative to sodium levels may identify an electrolyte-deplete acute decompensated HF (ADHF) phenotype with different prognostic consequences. This study aimed to determine the independent and incremental long-term prognostic impact of admission serum chloride levels after hospitalization for ADHF.

## METHODS

**STUDY POPULATION AND DATA SYNTHESIS.** The Cleveland Clinic Institutional Review Board approved this study. We identified 1,318 unique, consecutive patients admitted to the internal medicine or cardiology inpatient services at the Cleveland Clinic between July 28, 2008, and December 31, 2013, with a discharge diagnosis of ADHF. We confirmed the discharge diagnosis by performing a search of the International Classification of Diseases-Ninth Revision codes for acute or chronic HF (428.x). To further improve the specificity of selecting an established chronic HF population, only patients with a documented prior cardiac implantable electronic device (implantable cardioverter-defibrillator [ICD] or cardiac resynchronization therapy) were retained in the registry. The presence of an ICD or cardiac resynchronization therapy device was confirmed if there was a prior medical encounter caused by such a device (V45.02), radiological examination suggesting the presence of an ICD or cardiac resynchronization therapy, electronic analysis of an ICD (including interrogation, evaluation of generator status or programming parameters, electrocardiographic analysis, or a wearable cardioverter-defibrillator system), or procedure in which there was a prior insertion or repositioning of an electrode lead for a single- or dual-chamber pacing ICD and insertion of a pulse generator.

Patients were excluded if they were not given a loop diuretic during admission, did not have an active medication list, were <18 years of age, had prior heart transplantation or mechanical circulatory assist device, or were on chronic dialysis therapy. Only the first admission for a patient was included in the cohort if they were subsequently readmitted. Long-term all-cause mortality was determined from the electronic medical record and validated, if possible, by the Social Security Death Index. All patients were followed until December 31, 2013.

**VALIDATION COHORT.** Charts of consecutive admissions to noninterventional cardiology or internal medicine services at the Hospital of the University of

Pennsylvania from 2004 to 2009 were reviewed. The assembly and characteristics of patients in this cohort have been previously described (14,15). Briefly, inclusion required a primary discharge diagnosis of congestive HF, a hospital admission length between 3 and 14 days, and a B-type natriuretic peptide level >100 pg/ml within 24 h of admission. Patients on renal-replacement therapy were excluded from analysis, as were patients without documentation of specific HF etiology, available blood chemistry values at admission, or baseline medication use information. As in the derivation cohort, in the case of multiple admissions for a single patient, only the first admission was included. Clinical, demographic, imaging, and laboratory data, and documented primary and secondary diagnoses were reviewed from the electronic medical record. Admission chloride was defined as the level on first blood draw on presentation; discharge chloride was determined using the blood draw on the day of discharge. All patients were followed until June 30, 2012, and death was verified by the Social Security Death Index.

**STATISTICAL METHODS.** Continuous variables were expressed as median (interquartile range) and categorical variables were expressed as percent. The Jonkheere-Terpstra and Cuzick methods were used to test trend across tertiles of admission chloride levels for continuous and categorical variables, respectively (16). Spearman correlation coefficients ( $\rho$ ) were used to show correlations between continuous variables. Survival analyses were completed via the Kaplan-Meier method and log-rank test to compare survival curves across admission chloride tertiles. Cox proportional hazards models were used to examine the association between chloride levels and time to all-cause mortality after adjusting for potential confounders. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were determined for all covariates. Proportional hazard assumption violations were estimated by generalized linear regression of scaled Schoenfeld residuals on time. For proportional hazard violations ( $p < 0.1$ ), “within-stratum” estimates were provided for models stratified by categorical variables, and Heaviside functions were used to determine the time-dependency of risk for continuous variables. The model covariates were selected a priori (based on previous prognostic reports in patients with HF and clinical experience) either because of their prognostic relevance or their potential to confound the chloride-risk relationship. These included admission sodium, blood urea nitrogen, length of stay (days), age (years), ischemic cardiomyopathy, beta-blocker use, renin-angiotensin system

inhibitor use, and mineralocorticoid antagonist use (17,18). The discrimination (C statistic) of the impact of chloride levels on mortality was determined as previously described (19). Category-free net-reclassification indexes and integrated discrimination improvement were calculated to further clarify the incremental prognostic value of chloride (20). Double-sided p values <0.05 were considered statistically significant. Statistical analyses were performed using Stata version 13.1 software (Stata-Corp LP, College Station, Texas).

## RESULTS

**BASELINE CHARACTERISTICS.** Baseline characteristics for the Cleveland Clinic and University of Pennsylvania cohorts are shown in Tables 1 and 2, respectively. For the Cleveland Clinic cohort, admission chloride levels were normally distributed, with median and mean admission chloride being 101 (interquartile range: 97 to 104) mEq/l and  $100 \pm 6$  mEq/l, respectively. As expected, admission chloride levels were directly correlated to admission sodium levels ( $p = 0.61$ ;  $p < 0.001$ ) and negatively correlated to admission bicarbonate levels ( $p = 0.39$ ;  $p < 0.001$ ). Higher chloride levels were positively associated with increasing LV ejection fraction, beta-blocker and renin-angiotensin system-blocker use, and renal dysfunction, but negatively associated with markers of neurohormonal activation (blood urea nitrogen and N-terminal pro-B-type natriuretic

peptide) and indicators of end-organ function (hemoglobin and bilirubin). They were also inversely related to length of stay in the hospital and net weight change during admission.

**CHLORIDE LEVELS AND ALL-CAUSE MORTALITY.** The Cleveland Clinic cohort of 1,318 patients had 2,261 person-years of follow-up for all-cause mortality. There were 359 deaths over a median follow-up time of 1.47 (interquartile range: 0.51 to 2.68) years. Kaplan-Meier survival estimates were different across tertiles of admission chloride level (log-rank  $p < 0.001$  for all) (Central Illustration). There were 164, 127, and 68 deaths for tertiles 1 to 3, respectively. Tertile 1 had a higher death incidence rate of 0.22 death/person-years compared with tertiles 2 and 3 with 0.14 and 0.10 death/person-years, respectively.

Per the univariable and multivariable proportional hazards models (Table 3), admission chloride levels were inversely associated with mortality ( $p < 0.001$ ). Every unit increase in chloride was associated with an ~6% relative improvement in survival (HR per unit change: 0.94; 95% CI: 0.92 to 0.95;  $p < 0.001$ ). Although admission sodium levels were also inversely associated with mortality (HR per unit change: 0.95; 95% CI: 0.93 to 0.97;  $p < 0.001$ ), admission chloride levels showed greater discrimination for mortality (C statistic: 0.60; 95% CI: 0.57 to 0.64) than admission sodium levels (C statistic: 0.56; 95% CI: 0.53 to 0.59;  $p < 0.001$ ). There was no

TABLE 1 Baseline Characteristics of the Cleveland Clinic Cohort

	Total (N 1,318)	Admission Chloride (mEq/l)			p Value*
		<99 (n 456)	99 to 103 (n 497)	>103 (n 365)	
Age, yrs	68.7 (59.1 to 77.2)	67.9 (59.2 to 76.2)	68.4 (58.7 to 77.3)	69.5 (60.1 to 78.2)	0.09
Male	70.0	71.9	69.8	67.7	0.19
Ischemic cardiomyopathy	34.8	33.6	38.2	31.5	0.64
LVEF, % (n 1,068)	27 (19 to 45)	25 (15 to 40)	25 (20 to 45)	34 (20 to 50)	<0.001
SBP, mm Hg	118 (105 to 137)	111 (102 to 128)	120 (105 to 137)	127 (113 to 144)	<0.001
Beta blocker	84.9	80.3	88.3	86.0	0.01
RAS blocker	59.2	52.2	62.2	63.8	<0.001
MRA	36.3	43.4	36.0	28.0	<0.001
Sodium, mEq/l	137 (135 to 140)	134 (131 to 137)	138 (136 to 149)	138 (138 to 142)	<0.001
Bicarbonate, mEq/l	25 (22 to 27)	27 (24 to 30)	25 (23 to 27)	23 (21 to 25)	<0.001
BUN, mg/dl	27 (19 to 40)	31 (22 to 47)	27 (19 to 38)	25 (18 to 34)	<0.001
Creatinine, mg/dl	1.28 (0.99 to 1.69)	1.33 (1.04 to 1.77)	1.29 (0.96 to 1.71)	1.20 (0.98 to 1.60)	0.004
NT proBNP, pg/ml (n 481)	4,817 (2,415 to 9,536)	5,793 (3,133 to 10,418)	4,268 (2,180 to 9,175)	4,684 (2,428 to 8,644)	0.044
Hemoglobin, g/dl	11.6 (10.1 to 13.1)	11.6 (10.2 to 13.2)	11.7 (10.2 to 13.2)	11.3 (9.7 to 12.7)	0.003
Total bilirubin, mg/dl	0.8 (0.5 to 1.3)	1.0 (0.6 to 1.5)	0.8 (0.5 to 1.3)	0.8 (0.5 to 1.1)	<0.001
Length of stay, days	8.7 (5.0 to 16.7)	9.7 (5.5 to 19.4)	9.0 (4.9 to 17.8)	7.9 (4.9 to 14.1)	<0.001
ΔWeight during admission, kg	2.5 ( -6.0 to 0.1)	2.9 ( -6.8 to 0.0)	2.8 ( -6.3 to 0.0)	1.5 ( -4.4 to 0.3)	<0.001

Values are median (interquartile range) or %. \*p value for the Jonckheere-Terstra or Cuzick tests of trend.

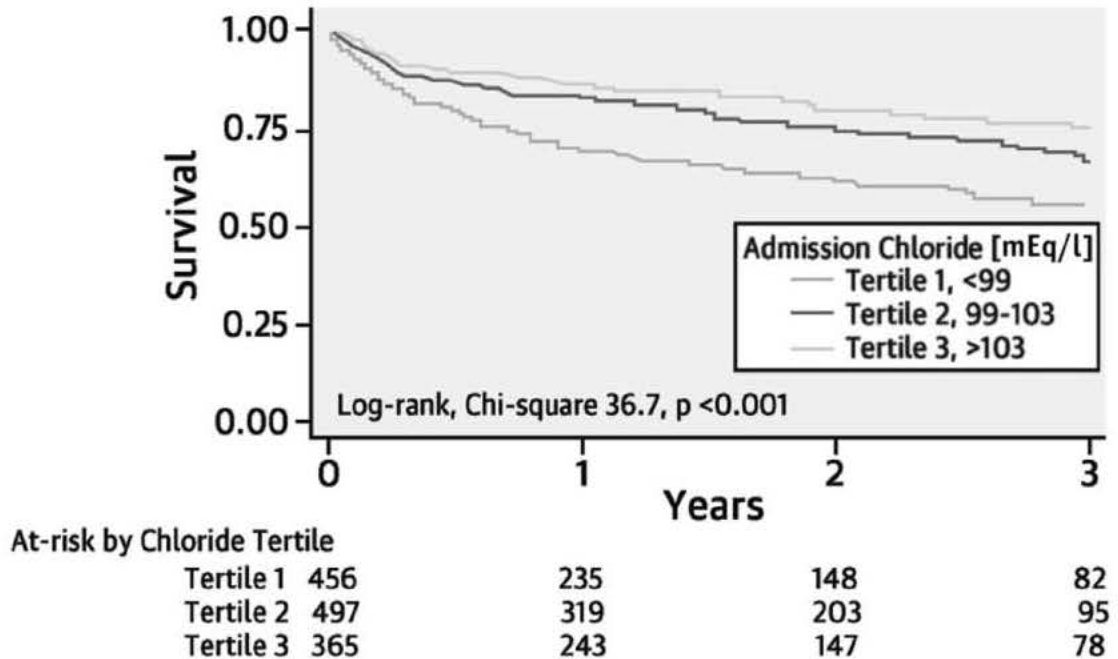
BUN blood urea nitrogen; LVEF left ventricular ejection fraction; MRA mineralocorticoid antagonist; NT-proBNP N-terminal pro-B-type natriuretic peptide; RAS renin-angiotensin system; SBP systolic blood pressure.

**TABLE 2** Baseline Characteristics of the University of Pennsylvania Cohort

	Total (N 876)	Admission Chloride (mEq/l)			p Value <sup>a</sup>
		<101 (n 253)	101 to 104 (n 262)	>104 (n 361)	
Age, yrs	62.9 (51.4 to 74.3)	64.9 (53.8 to 74.8)	59.2 (48.3 to 72.7)	64.5 (52.3 to 75.6)	0.67
Male	54.3	60.1	59.2	46.8	0.001
Ischemic cardiomyopathy	24.2	33.6	16.8	23.0	0.01
LVEF, %	27.5 (15 to 47.5)	27.5 (15 to 50)	25 (15 to 45)	30 (15 to 47.5)	0.48
SBP, mm Hg	135 (115 to 158)	120 (102 to 143)	138 (118 to 161)	145 (126 to 166)	<0.001
Beta blocker	67.4	71.5	66.4	65.1	0.10
RAS blocker	61.2	60.9	63.7	59.6	0.67
MRA	15.1	22.5	14.1	10.5	<0.001
Sodium, mEq/l	139 (137 to 141)	136 (133 to 139)	139 (137 to 141)	141 (139 to 142)	<0.001
Bicarbonate, mEq/l	25 (23 to 28)	28 (25 to 31)	26 (24 to 28)	24 (21 to 26)	<0.001
BUN, mg/dl	22 (15 to 34)	30 (18 to 48)	20.5 (15 to 27)	21 (14 to 33)	<0.001
Creatinine, mg/dl	1.3 (1.0 to 1.7)	1.40 (1.0 to 1.8)	1.2 (1.0 to 1.5)	1.3 (1.0 to 1.7)	0.19
BNP, pg/ml	1,314 (673 to 2,435)	1,372 (715 to 2,845)	1,241 (649 to 2,113)	1,319 (671 to 2,389)	0.86
Hemoglobin, g/dl	12.3 (10.7 to 13.6)	12.2 (10.6 to 13.7)	12.6 (11.0 to 13.9)	12.1 (10.6 to 13.5)	0.44
Total bilirubin, mg/dl	0.8 (0.5 to 1.4)	0.9 (0.6 to 1.7)	0.9 (0.5 to 1.4)	0.7 (0.4 to 1.0)	<0.001
Length of stay, days	5 (4 to 8)	6 (4 to 9)	5 (4 to 8)	5 (4 to 7)	<0.001
ΔWeight during admission, kg	3.1 ( 5.9 to 0.8)	2.6 ( 5.9 to 0.7)	3.2 ( 6.4 to 0.9)	3.4 ( 5.4 to 0.7)	0.55

Values are median (interquartile range) or %. <sup>a</sup>p value for the Jonckheere-Terstra or Cuzick tests of trend.  
 BNP B-type natriuretic peptide; other abbreviations as in Table 1.

**CENTRAL ILLUSTRATION** Chloride in Acute Decompensated Heart Failure: Survival Estimates by Admission Chloride Levels



Grodin, J.L. et al. J Am Coll Cardiol. 2015; 66(6):659-66.

For the Cleveland Clinic cohort, Kaplan Meier survival estimates significantly differed across tertiles of admission chloride level (log rank  $p < 0.001$ ), with worse survival for lower admission chloride levels.

significant interaction between admission chloride and sodium levels for mortality ( $p = 0.19$ ). Kaplan-Meier survival estimates stratified by admission hypochloremia (chloride  $<96$  mEq/l) and hyponatremia (sodium  $<134$  mEq/l) are shown in Figure 1, which graphically illustrates that chloride levels may have a stronger prognostic role than sodium levels.

After multivariable adjustment, admission chloride levels remained independently inversely associated with mortality (HR per unit change: 0.93; 95% CI: 0.90 to 0.97;  $p < 0.001$ ) (Figure 2). Mortality risk increased with decreasing chloride levels below  $\sim 96$  mEq/l and did not significantly differ at values  $>96$  mEq/l. There was no increase in the overall C statistic of the multivariable model with the addition of chloride (0.68 vs. 0.69;  $p = 0.5$ ). However, adding chloride to the multivariable model did significantly reclassify risk (integrated discrimination improvement, 10%;  $p < 0.001$ ; category-free net-reclassification indexes, 17.2%;  $p = 0.006$ ). With additional adjustment for weight change and blood urea nitrogen/creatinine ratio, admission chloride levels remained significantly associated with mortality (HR per unit change: 0.93; 95% CI: 0.90 to 0.97;  $p < 0.001$ ).

However, after multivariable adjustment for other variables including admission chloride levels, admission sodium levels were not independently associated with mortality (HR per unit change: 1.03; 95% CI: 0.99 to 1.07;  $p = 0.18$ ). Discharge chloride level was significant when substituted for admission chloride level (discharge sodium level was substituted for admission sodium level) in the multivariable model for mortality (HR per unit change: 0.94; 95% CI: 0.92 to 0.97;  $p < 0.001$ ) and is graphically depicted in Figure 3.

To validate our present findings, we turned to an independent acute HF cohort from the University of Pennsylvania with longer follow-up (Table 3). Admission chloride distribution was comparable with our study cohort (median: 103 [100 to 106] mEq/l; mean:  $103 \pm 6$  mEq/l). Baseline characteristics of this validation cohort are presented in Table 2. Similar to the Cleveland Clinic cohort, admission chloride levels were directly correlated to admission sodium ( $p = 0.54$ ;  $p < 0.001$ ) and negatively correlated to admission bicarbonate levels ( $p = -0.49$ ;  $p < 0.001$ ). There were 453 deaths out of 876 patients with 3,038 person-years of follow-up for all-cause mortality. In contrast to the derivation cohort, admission chloride levels violated the proportional hazards assumption ( $p > 0.1$ ) and were thus analyzed as a Heaviside function with time stratified at 1 year. Admission chloride levels were inversely associated with 1-year mortality in unadjusted (HR per unit change: 0.93; 95% CI: 0.91 to 0.95;

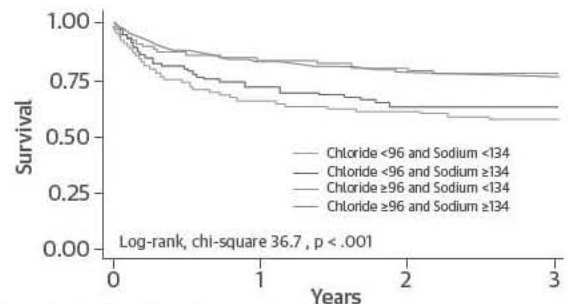
TABLE 3 Univariable and Multivariable Cox Proportional Hazards Models for Mortality

	Univariable			Multivariable		
	HR	95% CI	p Value	HR	95% CI	p Value
<b>Cleveland Clinic Cohort</b>						
Chloride, mEq/l	0.94	0.92 0.95	$<0.001$	0.93*	0.90 0.97	$<0.001$
Sodium, mEq/l	0.95	0.93 0.97	$<0.001$			
Log BUN, mg/dl	2.59	2.14 3.14	$<0.001$	2.00*	1.61 2.48	$<0.001$
Ischemic cardiomyopathy	1.36	1.10 1.68	0.004			
Beta blocker	0.74	0.56 0.97	0.028			
RAS blocker	0.77	0.63 0.95	0.015			
SBP, mm Hg	0.991	0.986 0.995	$<0.001$	0.993*	0.988 0.998	0.01
Age, yrs	1.02	1.01 1.03	$<0.001$	1.02*	1.01 1.03	$<0.001$
Bicarbonate, mEq/l	1.03	1.01 1.06	0.011			
Length of stay, days	1.002	0.999 1.005	0.14			
<b>University of Pennsylvania Cohort</b>						
Chloride, mEq/l, $\leq 1$ yr	0.93†	0.91 0.95	$<0.001$	0.95†	0.92 0.99	0.01
Chloride, mEq/l, $>1$ yr	0.99†	0.97 1.02	0.56			
Sodium, mEq/l	0.96	0.94 0.98	$<0.001$			
Log BUN, mg/dl	2.13	1.83 2.48	$<0.001$	1.60	1.34 1.91	$<0.001$
Ischemic cardiomyopathy	1.48	1.21 1.81	$<0.001$			
Beta blocker	1.15	0.94 1.41	0.16			
RAS blocker	0.96	0.79 1.15	0.63			
MRA	1.14	0.88 1.47	0.33			
SBP, mm Hg	0.994	0.991 0.997	$<0.001$	0.996	0.992 0.999	0.01
Age, yrs	1.032	1.026 1.039	$<0.001$	1.03	1.02 1.04	$<0.001$
Bicarbonate, mEq/l	1.01	0.99 1.03	0.337			
Length of stay, days	1.05	1.02 1.08	0.001	1.03	1.00 1.07	0.04

\*Within-stratum estimate stratified by MRA use. †HRs reported for both Heaviside functions in same model. CI confidence interval; HR hazard ratio; other abbreviations as in Table 1.

$p < 0.001$ ) and adjusted analysis (HR per unit change: 0.95; 95% CI: 0.92 to 0.99;  $p = 0.01$ ). Additionally, the adjusted association with admission sodium levels was not significant (HR per unit change: 0.99; 95% CI:

FIGURE 1 Survival Estimates Stratified by Admission Hypochloremia and Hyponatremia

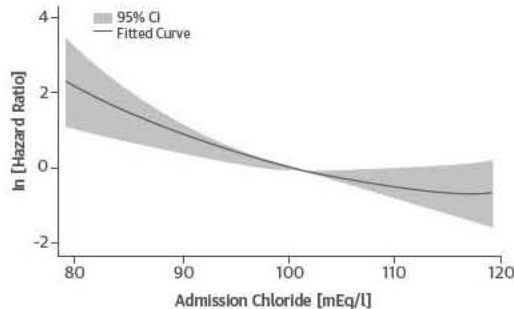


At-risk by Chloride and Sodium Level [mEq/l]	0	1	2	3
Chloride $<96$ and Sodium $<134$	148	97	91	85
Chloride $<96$ and Sodium $\geq 134$	86	61	55	54
Chloride $\geq 96$ and Sodium $<134$	84	71	67	66
Chloride $\geq 96$ and Sodium $\geq 134$	1000	838	791	766

Kaplan Meier survival curve estimates classified by levels of chloride ( $<$  or  $\geq 96$  mEq/l) and sodium ( $<$  or  $\geq 134$  mEq/l) on admission demonstrate that chloride levels may provide a stronger prognosis role than sodium levels.



**FIGURE 2 Mortality Risk per Adjusted Admission Chloride Levels**



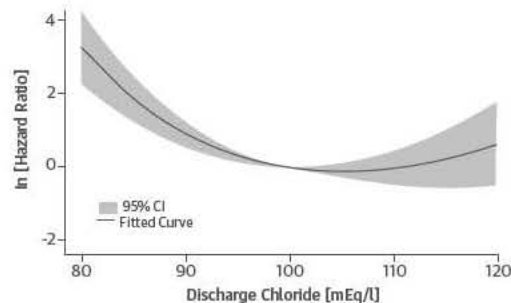
A fitted curve was generated from residual estimates according to admission chloride level at the Cleveland Clinic after multi variable adjustment for sodium, length of stay, bicarbonate, blood urea nitrogen, age, ischemic cardiomyopathy, and drug use (beta blocker, renin angiotensin system blocker, and mineralo corticoid antagonist). CI confidence interval.

0.96 to 1.03;  $p = 0.58$ ). Similar to the Cleveland Clinic cohort, discharge chloride level was significant when substituted for admission chloride level (discharge sodium level was substituted for admission sodium level) to the multivariable model for mortality (HR per unit change: 0.97; 95% CI: 0.95 to 0.99;  $p = 0.01$ ).

## DISCUSSION

In 2 contemporary cohorts of patients predominantly with systolic dysfunction hospitalized for

**FIGURE 3 Mortality Risk per Adjusted Discharge Chloride Levels**



A fitted curve was generated from residual estimates according to discharge chloride level at the Cleveland Clinic after multi variable adjustment for sodium, length of stay, bicarbonate, blood urea nitrogen, age, ischemic cardiomyopathy, and drug use (beta blocker, renin angiotensin system blocker, and mineralo corticoid antagonist). CI confidence interval.

ADHF and electrolyte measures, we report several key findings that highlight prognostic implications of serum chloride. First, serum chloride levels were independently and inversely associated with mortality after multivariable adjustment for other prognostic factors including serum sodium concentration. Second, serum chloride levels modestly enhanced mortality prediction compared with sodium levels. Furthermore, serum sodium levels were no longer associated with mortality when serum chloride levels were added to the multivariable model. Finally, although modestly correlated, serum chloride and serum sodium levels had no significant interaction for mortality prediction. These findings highlight the prognostic implications of serum chloride level in ADHF and suggest that it provides stronger prognostic information than serum sodium level. Further investigations into the clinical relevance of hypochloremia in the setting of acute HF are warranted.

The pathological role of chloride in HF is incompletely understood, in part because chloride levels have been rarely documented in clinical trials or registries. Chloride accounts for approximately one-third of the tonicity and two-thirds of all negative charges in the plasma (21). Dietary sodium chloride is the main source of chloride in the body and its removal is facilitated by gastric, sweat, and renal excretion. Serum chloride levels may represent the downstream effects of adversely prognostic maladaptive neurohormonal, renal, and acid-base disturbances in HF. Indeed, mechanisms that reduce sodium levels can similarly lower chloride levels (22). These include: 1) the pathological impairment of free water excretion resulting from increased nonosmotic release of arginine vasopressin (23), which is typically increased in patients with symptomatic HF (24,25); 2) the pleotropic effects of excess angiotensin II on renal sodium and water handling and neural thirst center activation (1); and 3) increased baroreceptor-mediated release of arginine vasopressin (24). All of these mechanisms are directly stimulated in HF (26). As a result, lower chloride levels may be dilutional in nature. Yet they may also represent a state of electrolyte depletion, especially when chloride is lower relative to sodium, which can occur in the setting of diuretic-induced salt wasting as chloride is excreted in the urine while bicarbonate is retained to maintain electro-neutrality (27). Making this distinction may have clinical implications when administering decongestive therapies for acute HF (28).

Both sodium and chloride levels were prognostically similar in unadjusted, but not adjusted,



analyses, potentially suggesting a pathophysiological difference in the 2 electrolytes. In the presence of HF, the relative concentrations of sodium and chloride in the plasma compartments can be lowered symmetrically or asymmetrically (29,30). This may be related to the ability of the kidney to excrete these electrolytes and modified by therapeutic measures (loop diuretics) and comorbid conditions. Chloride is a buffer for cations, including acid and sodium, and plays a major role in the ability of the kidney to eliminate salt and water. Therefore, in contrast to sodium, chloride has a stronger prognostic role because it may play a broader homeostatic role.

Our finding that lower chloride levels during admission were associated with higher mortality offers important insights into interpretation of electrolytes in ADHF. Our findings suggest that although sodium levels are important, more robust prognostic information can be inferred from serum chloride levels. Although low sodium has consistently been shown to be a strong predictor of short- and long-term morbidity and mortality in patients with both systolic and diastolic HF (7,11,13,31,32), there was little mention of the impact of chloride on the interpretation of sodium levels in these analyses. As our results suggest, these previous results may have failed to take into account serum chloride levels. Prior evidence for the prognostic role of chloride is sparse, and there is no formalized definition of hyponatremia in HF. Our observations highlight the need to focus on better understanding of chloride homeostasis and preserving it as a potential therapeutic consideration, particularly in the setting of ADHF with extensive use of loop diuretics that primarily inhibit the sodium-potassium-chloride cotransporter leading to inevitable and excessive chloride wasting.

**STUDY LIMITATIONS.** Our results must be interpreted in the context of several limitations in our study design. We cannot exclude the presence of selection bias for those undergoing evaluation and treatment for ADHF at 2 tertiary care centers. However, the external validity of these findings is strengthened with the addition of the validation cohort. These patients largely had systolic dysfunction with questionable generalizability to an ADHF population with preserved LV systolic function. Yet this also afforded an opportunity for a diversity of pathology in a contemporary cohort recorded by a modern electronic medical record to be retrieved in a very efficient manner. Our analysis also displayed a unique way of identifying patients presenting

with ADHF and established HF based on the history of an ICD. Data were lacking regarding patient-level decision making and resulting medication changes and the impact they would have on changing chloride levels and prognosis. Similarly, the impact of chloride levels on HF rehospitalizations 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 hyperchloremia. To our knowledge, however, therapies that increase serum chloride concentrations, such as hypertonic saline, are rarely used in ADHF populations, but the potential impact of potassium supplementation with potassium chloride is unclear. Nevertheless, this large, well-powered ADHF cohort confers a new perspective on serum chloride levels and their impact on prognosis.

## CONCLUSIONS

Serum chloride levels measured during hospitalization for ADHF are independently and inversely associated with long-term mortality. This association was independent of, and added incremental prognostic information to, serum sodium levels. These findings highlight the clinical significance of chloride, a routinely measured electrolyte, in long-term prognostication for ADHF.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL

**SKILLS:** Like hyponatremia, hypochloremia in patients hospitalized for ADHF is independently associated with long-term mortality.

**TRANSLATIONAL OUTLOOK:** Additional clinical and mechanistic studies are needed to investigate the pathophysiology of electrolyte depletion in patients with ADHF and develop therapeutic strategies that avoid the adverse consequences associated with hypochloremia.

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