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Prognostic Role of Serum Chloride Levels in Acute Decompensated Heart Failure

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ABSTRACT

BACKGROUND Acute decompensated heart failure (ADHF) can be complicated by electrolyte abnormalities, but the major focus has been concentrated on the clinical significance of serum sodium levels.

OBJECTIVES This study sought to determine the prognostic significance of serum chloride levels in relation to serum sodium levels in patients with ADHF.

METHODS We reviewed 1,318 consecutive patients with chronic heart failure admitted for ADHF to the Cleveland Clinic between July 2008 and December 2013. We also validated our findings in an independent ADHF cohort from the University of Pennsylvania (n = 876).

RESULTS Admission serum chloride levels during hospitalization for ADHF were independently and inversely associated with long-term mortality (hazard ratio [HR] per unit change: 0.94; 95% confidence interval [CI]: 0.92 to 0.95; $p < 0.001$). After multivariable risk adjustment, admission chloride levels remained independently associated with mortality (HR per unit change: 0.93; 95% CI: 0.90 to 0.97; $p < 0.001$) in contrast to admission sodium levels, which were no longer significant ($p > 0.05$). Results were similar in the validation cohort in unadjusted (HR per unit change for mortality risk within 1 year: 0.93; 95% CI: 0.91 to 0.95; $p < 0.001$) and multivariable risk-adjusted analysis (HR per unit change for mortality risk within 1 year: 0.95; 95% CI: 0.92 to 0.99; $p = 0.01$).

CONCLUSIONS These observations in a contemporary advanced ADHF cohort suggest that serum chloride levels at admission are independently and inversely associated with mortality. The prognostic value of serum sodium in ADHF was diminished compared with chloride. (J Am Coll Cardiol 2015;66:659-66) © 2015 by the American College of Cardiology Foundation.

Heart 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).

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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

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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 (ρ) 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