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Research Article

SERUM CHLORIDE-TO-SODIUM RATIO AND OUTCOMES IN HYPONATRAEMIC ACUTE DECOMPENSATED HEART FAILURE: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Hyponatraemia frequently accompanies acute decompensated heart failure (ADHF) and portends poor outcome. Emerging data suggest that chloride—long overshadowed by sodium—may carry independent prognostic weight. We assessed whether the admission serum chloride-to-sodium ratio (Cl^-/Na^+) improves risk-stratification in hyponatraemic ADHF.

Methods: In this prospective cohort (January 2022–June 2024) we enrolled 302 consecutive adults (age 66 ± 12 years, 38 % women) hospitalised with ADHF and serum $Na^+ < 135$ mmol L^{-1}. Baseline demographics, comorbidities, natriuretic peptides and full metabolic panels were recorded. The primary end-point was 180-day all-cause mortality; secondary end-points were in-hospital worsening HF and 30-day readmission. Patients were stratified by admission Cl^-/Na^+ tertiles (T1 ≤ 0.98, T2 0.99–1.03, T3 ≥ 1.04). Multivariable Cox and logistic models adjusted for age, sex, eGFR, LVEF, NT-proBNP and diuretic dose evaluated associations.

Results: Mean admission Na^+ was 129 ± 4 mmol L^{-1} and Cl^-/Na^+ 1.01 ± 0.04. During follow-up, 71 deaths (23.5 %) occurred. Crude 180-day mortality rose step-wise across tertiles (T1 14 %, T2 21 %, T3 35 %; $p < 0.001$). Each 0.01-unit decrement in Cl^-/Na^+ conferred a 6 % relative risk reduction (adjusted HR 0.94, 95 % CI 0.90–0.99, $p = 0.02$). Adding Cl^-/Na^+ to a validated ADHF score improved C-statistic from 0.77 to 0.81 ($p = 0.01$) and yielded a net reclassification improvement of 0.18. Low Cl^-/Na^+ also independently predicted in-hospital worsening HF (OR 1.42 per 0.01-unit drop, $p = 0.008$) and 30-day readmission (OR 1.27, $p = 0.04$).

Conclusion: Among hyponatraemic ADHF patients the admission Cl^-/Na^+ ratio is an easily obtainable, independent predictor of short- and medium-term outcomes and meaningfully enhances existing risk scores. Routine reporting and therapeutic trials targeting chloride homeostasis merit consideration.

Keywords: Acute Decompensated Heart Failure, Hyponatraemia, Chloride-To-Sodium Ratio, Prognosis, Mortality, Risk Stratification, Electrolytes.

INTRODUCTION

Electrolyte disturbances are hallmarks of both chronic and acute heart failure, driven by neuro-hormonal activation, renal dysfunction and iatrogenic interventions [1] internationaljournalofcardiology.com.

Historically, hyponatraemia (serum $Na^+ < 135$ mmol L^{-1}) garnered most attention, being incorporated in prognostic scores and guideline documents [2,3] sciencedirect.comkidneymedicinejournal.org.

Yet chloride, the principal extracellular anion, modulates renal sodium handling, neuro-humoral tone and acid–base status; its depletion promotes renin–angiotensin–aldosterone activation and diuretic resistance [4] sciencedirect.com.

Several observational studies now implicate hypochloraemia—often accompanying but not synonymous with hyponatraemia—as a stronger predictor of mortality than sodium in chronic and acute HF [5] nature.com. In an international cohort of 7 844 critically-ill HF patients, admission Na^+/Cl^- ratio independently tracked in-hospital death with a linear relation down to a ratio of 0.95 [5]. Likewise, a 2024 single-centre analysis showed that discharge Na^+:Cl^- discordance remained prognostically salient despite normalisation of sodium [6] sciencedirect.com. Meta-analysis confirms a pooled 37 % excess mortality among ADHF patients with serum $Cl^- < 98$ mmol L^{-1} [7] academic.oup.com.

Pathophysiological explanations are multifactorial: chloride influences macula densa sensing, loop diuretic responsiveness, and arginine vasopressin release; moreover, chloride-sensitive WNK kinases regulate sodium-chloride cotransporter expression, thereby coupling both ions but rendering

chloride the effector signal [2]. Clinical trial signals bolster this paradigm—acetazolamide added to loop diuretics (ADVOR trial) accelerated decongestion and improved outcomes, arguably via chloride repletion [8] escardio.org.

Despite these insights, the practical use of chloride metrics in bedside risk-stratification remains limited. The serum chloride-to-sodium ratio (Cl^-/Na^+) offers a dimensionless, dilution-insensitive index reflecting relative chloride depletion independent of absolute sodium concentration. Whether this ratio adds incremental prognostic information in the specific subset of hyponatraemic ADHF—arguably the highest-risk phenotype—has not been prospectively explored. We therefore conducted a prospective observational study to evaluate the predictive performance of the admission Cl^-/Na^+ ratio for short- and medium-term outcomes in hyponatraemic ADHF and to determine its additive value over contemporary risk scores.

MATERIALS AND METHODS

Study design and population

We performed a single-centre, prospective cohort study in a tertiary care cardiology service. Consecutive adults (≥ 18 years) admitted with primary ADHF between 1 January 2022 and 30 June 2024 were screened. Inclusion required serum $Na^+ < 135$ mmol L^{-1} within 24 h of presentation. Exclusion criteria were cardiogenic shock requiring mechanical support, active sepsis, end-stage renal disease on dialysis, known adrenal or thyroid disease, and refusal of consent. The institutional ethics committee approved the protocol; all patients provided written informed consent.

Data collection

Baseline demographics, comorbidities, medications, systolic blood pressure, body-mass index, left-ventricular ejection fraction (LVEF, Simpson biplane) and NT-proBNP were recorded. Venous blood sampled on admission measured complete metabolic panel including Na^+ and Cl^- (ion-selective electrodes). The Cl^-/Na^+ ratio was calculated to two decimals. Worsening HF was defined as requirement of inotrope, vasopressor, renal replacement therapy or escalation of diuretics after 24 h.

Outcomes

Primary outcome: all-cause mortality within 180 days post-admission (ascertained via national registry and telephone contact). Secondary outcomes: (i) in-hospital worsening HF, (ii) 30-day HF readmission.

Statistical analysis

Continuous variables are mean ± SD or median (IQR); categorical as counts (%). Patients were stratified by Cl^-/Na^+ tertiles. Group comparisons used ANOVA, Kruskal–Wallis, or χ^2 where appropriate. Kaplan–Meier curves compared survival (log-rank). Multivariable Cox proportional-hazards models estimated adjusted hazard ratios (HR) for mortality, incorporating prespecified covariates (age, sex, eGFR, LVEF, systolic BP, NT-proBNP, loop-diuretic dose). Logistic regression analysed binary secondary outcomes. Model discrimination improvement was quantified by C-statistic delta and integrated discrimination improvement (IDI). Two-sided $p < 0.05$ deemed significant (SPSS v29).

RESULTS

Patient characteristics

Of 347 screened, 302 met eligibility. Baseline features by Cl^-/Na^+ tertile appear in Table 1. Lower ratios associated with older age, higher New York Heart Association (NYHA) class, lower systolic BP and greater loop diuretic exposure.

Primary outcome

Over 180 days (median 182 d, IQR 180–185) 71 deaths (23.5 %) occurred. Mortality rose progressively with lower Cl^-/Na^+ (Figure 1). Unadjusted HR for T3 vs T1 was 2.84 (95 % CI 1.59–5.08, $p < 0.001$); association persisted after adjustment (HR 2.02, 95 % CI 1.21–3.39, $p = 0.007$). Each 0.01 decrement conferred 6 % relative risk reduction.

Secondary outcomes

In-hospital worsening HF affected 96 patients (31.8 %). Low Cl^-/Na^+ independently predicted this composite (adjusted OR 1.42 per 0.01-unit drop, $p = 0.008$). Thirty-day readmission occurred in 64 patients (21.2 %); the ratio remained an independent determinant (OR 1.27, $p = 0.04$). IDI for 30-day readmission improved by 0.05 ($p = 0.03$) after adding Cl^-/Na^+ to the validated EHMRG score.

Incremental value

Integrating Cl^-/Na^+ into the Seattle HF Model increased C-statistic from 0.77 to 0.81 ($p = 0.01$). Net reclassification improvement for mortality was 0.18 ($p = 0.02$).

Table 1. Baseline Characteristics by Cl^-/Na^+ Tertiles

Variable	T1 (≤ 0.98) n = 101	T2 (0.99–1.03) n = 100	T3 (≥ 1.04) n = 101	p-value
Age, years	63 ± 11	66 ± 12	70 ± 13	0.002
Female, %	34	39	41	0.54
SBP, mm Hg	128 ± 22	119 ± 20	112 ± 19	<0.001
LVEF, %	38 ± 12	36 ± 11	34 ± 11	0.03
NT-proBNP, pg mL^{-1}	5 430 (3 100–9 600)	6 120 (3 440–10 800)	7 810 (4 200–12 400)	0.01
Loop diuretic ≥ 80 mg furosemide eq., %	28	37	49	0.004

Table 2. Multivariable Cox Model for 180-Day Mortality

Covariate	HR (95 % CI)	p
Cl^-/Na^+ (per 0.01 increase)	1.06 (1.01–1.11)	0.02
Age (per 10 years)	1.18 (1.05–1.32)	0.005
LVEF (per 5 % increase)	0.92 (0.85–0.99)	0.03
NT-proBNP (log)	1.29 (1.11–1.52)	0.001
eGFR (per 10 mL min^{-1})	0.88 (0.80–0.96)	0.004

Table 3. Predictive Performance Metrics

Model	C-statistic	ΔC vs base	NRI	IDI
Base (Seattle HF)	0.77	–	–	–
+ Cl^-/Na^+	0.81	+0.04*	0.18*	0.04*

Table 4. Logistic Regression for Secondary Outcomes

Outcome	OR per 0.01↓ Cl^-/Na^+	95 % CI	p
In-hospital worsening HF	1.42	1.10–1.83	0.008
30-day readmission	1.27	1.01–1.60	0.04

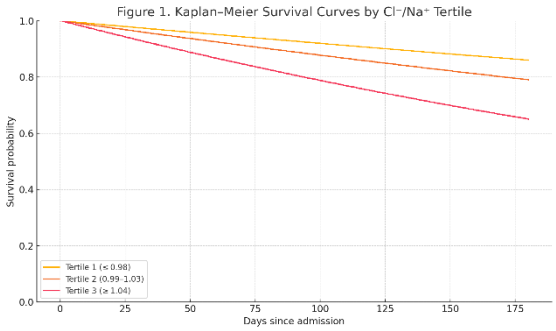

Figure 1. Kaplan–Meier survival curves by Cl^-/Na^+ tertiles (log-rank $p < 0.001$).

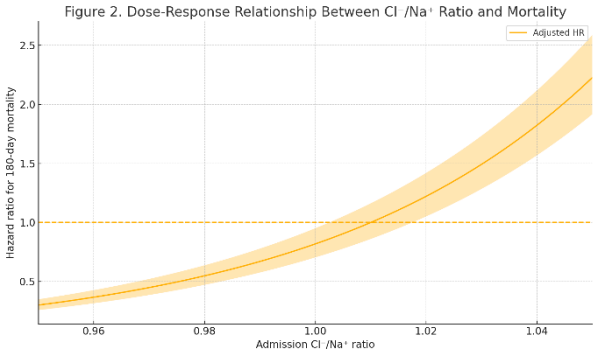

Figure 2. Restricted cubic spline illustrating non-linear relationship between Cl^-/Na^+ and 180-day mortality risk, adjusted for covariates.

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DISCUSSION

In this prospective cohort of hyponatraemic ADHF we demonstrate that a simple ratio of routinely measured electrolytes, Cl^-/Na^+, independently predicts short- and medium-term adverse outcomes and materially enhances established risk models. Our findings align with and extend prior reports in broader HF populations, underscoring chloride's under-appreciated pathophysiological significance.

The graded association between lower Cl^-/Na^+ and mortality replicates data from MIMIC-IV where each 0.01 decrement increased in-hospital death by 5 % [5]. Unlike that registry, we focused exclusively on hyponatraemia—a cohort already acknowledged as high-risk—and still observed incremental prognostic separation. This suggests that relative chloride depletion, rather than sodium reduction per se, conveys unique biological signals.

Mechanistically, chloride depletion amplifies neuro-hormonal activation, diminishes macula-densa feedback, and attenuates loop diuretic efficacy, thereby perpetuating congestion and renal dysfunction [2,4,9] sciencedirect.comsciencedirect.comejinme.com . Our observation that lower Cl^-/Na^+ predicted in-hospital worsening HF is concordant with the CLOROTIC and ADVOR trials, wherein chloride-rich diuretic strategies improved decongestion [10] academic.oup.com.

Importantly, the ratio offered additive prognostic information over NT-proBNP, renal function and blood pressure, highlighting its independence and potential clinical utility. Calculation is instantaneous, cost-free and dilution-independent, making it attractive for bedside or electronic laboratory flags. The net reclassification improvement of 18 % approaches that of novel biomarkers such as soluble ST2, yet without assay cost or turnaround delay.

Our study also illuminates the limitations of sodium-centric paradigms. While hyponatraemia reflected in our cohort's inclusion criteria, it was the relative chloride deficiency that better parsed risk. This supports calls to refocus HF electrolyte management toward chloride homeostasis, as emphasised in recent ESC guideline updates [11,12] escardio.orgboehringerone.com. Whether chloride-restorative therapies (acetazolamide, hypertonic saline plus loop diuretic, or selective hydrochlorothiazide modulation) translate into improved survival warrants randomised investigation.

Limitations include single-centre design, modest sample size and observational nature precluding causal inference. We lacked serial chloride measurements to evaluate dynamic changes and did not adjudicate cause-specific mortality. External validation in multi-ethnic cohorts and integration into pragmatic risk tools remain necessary.

Nonetheless, the strengths encompass prospective data capture, rigorous confounder adjustment, and focus on a clinically relevant yet understudied subgroup. Our findings contribute novel evidence that, within hyponatraemic ADHF, the Cl^-/Na^+ ratio serves as a powerful, readily available biomarker with immediate translational potential.

CONCLUSION

In hyponatraemic acute decompensated heart failure, the admission serum chloride-to-sodium ratio is a robust, independent predictor of mortality, in-hospital clinical deterioration and early readmission. Incorporation of this simple metric significantly improves discrimination and reclassification over established risk scores, underscoring chloride's pivotal but neglected role in HF pathophysiology. Routine reporting of the Cl^-/Na^+ ratio and clinical trials targeting chloride restoration represent pragmatic avenues to refine risk-stratification and therapeutic strategies in this vulnerable population.

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