Original Article

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Internal Medicine Section

Admission Serum Chloride Level as Predictor of Length of Stay in Acute Decompensated Heart Failure: A Prospective Observational Study

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ABSTRACT

Introduction: Acute Decompensated Heart Failure (ADHF) frequently results in hospitalisation and is associated with significant morbidity. Recent evidence suggests that admission serum chloride levels may offer prognostic value beyond traditional markers such as sodium or natriuretic peptides.

Aim: To assess the admission serum chloride level as predictor of length of stay in ADHF.

Materials and Methods: This prospective observational study was conducted at the Department of General Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, India, from August 2020 to May 2023, enrolled 60 adults (18-85 years) admitted with ADHF as defined by Modified Framingham criteria and Echocardiographic (ECHO) confirmation following ethical approval from the Institution. Informed consent was obtained from all participants. On admission, serum chloride and other blood parameters were measured. Serum chlorides levels were categorised as hypochloremia (<97 mEq/L), normochloremia (98-106 mEq/L), or hyperchloremia (≤107 mEq/L). The length of hospitalisation was recorded. The association between chloride and length of the stay was analysed using Analysis of Variance (ANOVA) in Statistical Package for Social Sciences (SPSS) version 25.0 and p-value <0.05 was considered significant.

Results: The mean age of the participants were 62.7±10.8 years, with 60% males. Hypochloremia patients (n=11) had longer stays (13.09±1.58 days) than normochloremic (n=20; 7.75±1.97 days) and hyperchloremic (n=29; 4.90±1.35 days) (p-value <0.001) groups. Admission serum sodium (p-value=0.008) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (p-value <0.001) varied significantly across chloride groups. There was strong negative correlation (r-value=-0.79; p-value <0.001) and the logistic regression showed that 1mEq/L increase in chloride cut the odds of prolonged stay by 53% (p-value=0.012) and confirms as a strong, independent predictor for length of hospital stay.

Conclusion: Admission hypochloremia predicts prolonged hospitalisation in ADHF, supporting chloride assessment for risk stratification. Overall, serum chloride provides stronger prognostic information for ADHF than traditional markers.

Keywords: Acid-base homeostasis, Electrolyte disturbances, Natriuretic peptide

INTRODUCTION

Heart Failure (HF) is a global public health challenge, affecting over 64 million individuals worldwide and imposing substantial morbidity, mortality, and healthcare costs [1]. Acute Decompensated Heart Failure (ADHF), is a complex and dynamic syndrome characterised by abrupt onset or gradual worsening of existing HF symptoms, including dysopnea, fluid overload, and fatigue, that often necessitates hospitalisation and requiring high rates of readmission [2,3]. Patients with ADHF exhibit a diverse clinical presentation, with majority requiring 7-10 days of in-hospital care under standard management protocols that includes diuretics, neurohormonal blockade, and supportive therapies [3]. A minority of patients diagnosed with ADHF exhibit low Blood Pressure (BP) (<8%) or shock (<3%) [3]. Despite advancements in pharmacotherapy and device management, these patients continue to face substantial morbidity [3].

Electrolyte disturbances are integral to ADHF pathophysiology, driven by both neurohormonal activation and decongestive therapies and influence the prognosis. While hyponatremia has traditionally received the most attention, serum chloride, an abundant but often understudied extracellular anion, plays a crucial role in maintaining electroneutrality, acid-base homeostasis, Renin-Angiotensin-Aldosterone (RAA) system regulation, and renal salt handling [4-9]. Importantly, loop and thiazide diuretics disproportionately lower chloride relative to sodium, thereby, impairing tubuloglomerular feedback and promoting diuretic resistance [4,10]. Ultimately, this increases the hospitalisation and mortality rate.

Seminal cohort studies have corroborated the independent association between low chloride levels at admission and adverse outcomes [11-13]. In a large US HF cohort, Grodin JL et al., found that lower serum chlorides were independently associated with increase mortality, while serum sodium levels lost significance after adjustment [11]. Subsequently, a retrospective analysis of 167 ADHF patients demonstrated that each 1mEq/L increased in admission chloride predicted a 1.3% shorter length of stay, independent of sodium levels [12]. Recent post-hoc analyses from the ADVOR trial (Acetazolamide in Decompensated HF with Volume Overload), showed that the use of adjunctive acetazolamide, a chloride-sparing diuretic, demonstrated that hypochloremia (≤97 mmol/L) at admission was independently associated with slower decongestion and prolonged hospital length of stay in ADHF patients [13].

The majority of existing literature has focused on mortality [11,14,15], however, the specific correlation between the admission serum chloride levels and length of the hospital stay in diverse and prospective populations remains underexplored. Additionally, variations in demographic and therapeutic contexts may affect these associations. As of this, this is the first prospective cohort study in an Indian tertiary care setting to assessing chloride alongside NT-proBNP. Therefore, the present study aimed to determine whether admission serum chloride levels independently predict the length of hospital stay in patients admitted with ADHF. The hypothesis that lower serum chloride at admission is independently associated with prolonged hospitalisation and that it may serve as a readily available biomarker to guide early risk stratification in ADHF.

MATERIALS AND METHODS

This prospective observational study was conducted at the Department of General Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, India, from August 2020 to May 2023. The study protocol received approval from the Institutional Human Ethics Committee (IHEC) (MGMCRI/Res/01/2020/24/IHEC/291) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Inclusion criteria: Patients aged 18-85 years with signs and symptoms of ADHF, as defined by the Modified Framingham criteria [16] and supported by ECHO findings as per the 2021 European Society of Cardiology (ESC) guidelines for acute and chronic HF [17]. These criteria included major indicators such as Paroxysmal Nocturnal Dyspnoea (PND), elevated Jugular Venous Pressure (JVP), orthopnoea, pulmonary rales, third heart sound (S3), cardiomegaly, and pulmonary oedema on chest radiograph; and minor criteria including peripheral oedema, nocturnal cough, exertional dyspnoea, hepatomegaly, pleural effusion, and tachycardia (>100 bpm).

Exclusion criteria: Patients receiving chronic dialysis therapy, those diagnosed with sepsis, or any known malignancy were excluded from the study.

Sample size calculation: Based on a retrospective analysis Goyal A et al., reported mean hospital stay of ADHF patients was 8.75 ±5.88 days among the patients at the time of admission for serum chloride assessment, and considering a 95% confidence level and a marginal error of 1.5 days, the sample size was calculated using the formula-

$$n=\left(\frac{Z_{1-\frac{\alpha}{2}}}{d}\right)^2$$

where Z1-α/2=1.96; α=5.88 and d=1.5 days, the sample size was 60. Sequential sampling was employed until the target was achieved [12].

Study Procedure

On admission of the patients, detailed demographic and clinical history was collected, followed by a comprehensive bedside clinical examination. All patients underwent routine diagnostic work-up. A 5mL venous blood samples was obtained for the laboratory work-up, including Complete Blood Count (CBC), renal and liver function tests, serum electrolytes, Arterial Blood Gas (ABG) analysis, Electrocardiogram (ECG), chest X-ray, Echocardiography (ECHO), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement within 24 hours of admission. Serum chloride values were stratified into three categories based on the Institutional laboratory reference ranges as: hypochloraemia (≤97 mEq/L), normochloremia (98-106 mEq/L), and hyperchloremia (≥107 mEq/L) [18].

The HF management was initiated based on standard guidelines, involving diuretics, antianginal agents, antihypertensives, and lipid-lowering medications as per 2021 ESC treatment recommendations [17]. Length of the hospital stay was defined as days from admission to discharge. Patients were considered fit for discharge upon meeting the following criteria: clinical improvement in Functional Class of HF (FC-HF), maintenance of systolic BP ≥90 mmHg, heart rate <80 bpm or <100 bpm in atrial fibrillation, oxygen saturation ≥95% {or ≥90% in Chronic Obstructive Pulmonary Disorder (COPD)} on room air, no inotropic or vasodilator requirement for over 24 hours, stable renal function, and successful transition from intravenous to oral diuretics [19,20]. Patients who were referred elsewhere, left Against Medical Advice (AMA), or succumbed to ADHF were excluded from the final analysis.

STATISTICAL ANALYSIS

Data were entered into MS Excel and analysed with SPSS version 25.0. Continuous variables are presented as mean±Standard Deviation (SD) or median {Interquartile Range (IQR)} and compared using One-way ANOVA or Kruskal-Wallis test as appropriate. Categorical variables are expressed as counts and percentages and compared using Chi-square test of Fisher's-Exact test. Pearsons's correlation and linear regression assessed the relationship between the serum chloride and length of stay. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Socio-demographic, co-morbidity, and clinical symptoms for the ADHF are presented in [Table/Fig-1], across three chloride level groups Hypochloremia (≤97 mEq/L); Normochloremia (98-106 mEq/L); Hyperchloremia (≥107 mEq/L). No significant difference was found between the groups for any clinical and demographic characteristics (p-value>0.05).

Characteristics	Hypochloraemia (<96 mEq/L) (n = 11)	Normochloremia (96-107 mEq/L) (n = 20)	Hyperchloremia (>107 mEq/L) (n = 29)	p-value
Age (years)	61.00±13.57	62.30±9.38	63.86±9.88	0.717[a]
Gender				
Female (n=36)	5 (13.9%)	14 (38.9%)	17 (47.2%)	0.401[b]
Male (n=24)	6 (25.0%)	6 (25.0%)	12 (50.0%)	
Alcoholic dependence				
No	6 (24.0%)	6 (24.0%)	13 (52.0%)	0.372[b]
Yes	5 (14.3%)	14 (40.0%)	16 (45.7%)	
Smoking				
No	6 (24.0%)	6 (24.0%)	13 (52.0%)	0.370[b]
Yes	5 (14.3%)	14 (40.0%)	16 (45.7%)	
Type 2 diabetes mellitus				
Yes	6 (22.2%)	5 (18.5%)	16 (59.3%)	0.881[b]
No	5 (15.2%)	15 (45.5%)	13 (39.4%)	
Systemic hypertension				
Yes	7 (26.9%)	10 (38.5%)	9 (34.6%)	0.136[b]
No	4 (11.8%)	10 (29.4%)	20 (58.8%)	
Pulmonary rales				
Yes	6 (27.3%)	12 (31.6%)	21 (55.3%)	0.267[b]
No	5 (13.2%)	8 (36.4%)	8 (36.4%)	
JVP elevation				
Yes	6 (25.0%)	13 (36.1%)	18 (50.0%)	0.541[b]
No	5 (13.9%)	7 (29.2%)	11 (45.8%)	
Cardiomegaly				
Yes	3 (14.3%)	5 (23.8%)	13 (61.9%)	0.301[b]
No	8 (20.5%)	15 (38.5%)	16 (41.0%)	
Peripheral oedema				
Yes	11 (27.5%)	11 (27.5%)	18 (45.0%)	0.304[b]
No	0	9 (45.0%)	11 (55.0%)	
Dyspnoea on exertion				
Yes	11 (27.5%)	11 (27.5%)	18 (45.0%)	0.304[b]
No	0	9 (45.0%)	11 (55.0%)	

[Table/Fig-1]: Clinical and demographic distribution across chloride level groups (N = 60).
[a]One-way ANOVA; [b]Chi-square test. p-value <0.05 were statistically significant and indicated in boldface. Continuous variables were expressed in mean±SD, while categorical variables were presented as number (percentage). JVP: Jugular venous pressure.

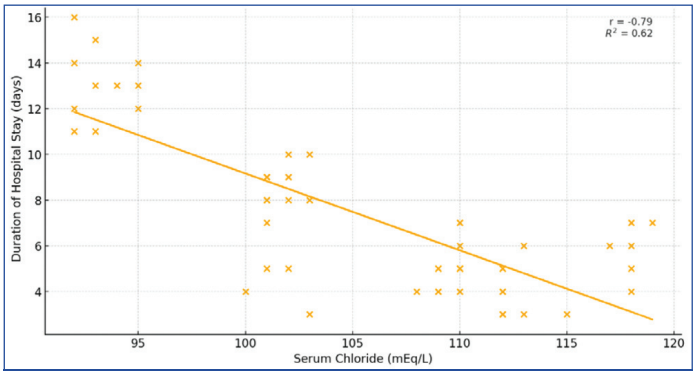
Haemodynamic parameters are presented in [Table/Fig-2] and resulted in no statistically significant differences observed in pulse rate, systolic and diastolic BP among the groups (p-value>0.05).

Serum sodium (Na) levels significantly differed across the chloride groups {F(2,57)=10.71; p-value=0.008}, with the highest sodium concentration observed in the ≥107 mEq/L group. Potassium (K), urea, and creatinine levels did not show significant variation (p-value >0.05). Notably, NT-proBNP levels showed a highly significant difference {F(2,57)=53.96; p-value <0.001}, with markedly elevated levels in the hypochloraemia group compared to others. A significant difference was observed in the duration of hospitalisation {F(2,57)=103.10; p-value <0.001}, with patients in the hypochloraemia group having a longer mean hospital stay (13.09±1.58 days) compared to the normochloremia and hyperchloremia [Table/Fig-2].

Variables	Hypochloraemia (<96 mEq/L) (n=11)	Normochloremia (96-107 mEq/L) (n=20)	Hyperchloremia (>107 mEq/L) (n=29)	p-value
Haemodynamic parameters				
Pulse rate (rpm)	81.55±9.73	83.35±4.42	85.93±8.62	0.295[a]
Systolic BP (mmHg)	112.73±11.90	112.50±12.51	119.66±13.75	0.119[a]
Diastolic BP (mmHg)	72.73±9.04	73.50±5.87	75.86±9.82	0.482[a]
Blood parameters				
Sodium (mEq/L)	127.91±5.43	131.55±6.94	138.55±6.72	0.008[a]
Potassium (mEq/L)	4.29±0.42	4.37±0.70	4.17±0.71	0.592[a]
Urea (mg/dL)	39.55±18.75	46.80±24.03	47.97±23.76	0.581[b]
Creatinine (mg/dL)	1.49±0.76	1.62±0.63	1.64±0.74	0.831[b]
NT-proBNP (pg/mL)	29005±8051.54	10146±7199.7	5668±4953.75	<0.001[a]
Length of hospital stay (days)	13.09±1.58	7.75±1.97	4.90±1.35	<0.001[a]

[Table/Fig-2]: Distribution of haemodynamic parameters, blood parameters, and length of hospital stay across serum chloride level groups.
[a]ANOVA; [b]Kurskal-Wallis. p-value <0.05 were statistically significant and indicated in boldface.
rpm: Rates per minute; BP: Blood pressure; NT-proBNP: N-terminal pro B-type natriuretic peptide

Pearson's correlation resulted a strong inverse relationship between the admission serum chloride and length of hospital stay (r-value=-0.79; p-value <0.001) [Table/Fig-3]. In multivariate linear regression {R2 0.76; F(4,55)=43.79; p-value <0.001}, each 1 mEq/L rise in admission serum chloride shortened hospital stay by 0.20 days (β-0.3; p-value <0.001), with NT-proBNP also independently associated with longer stays (β=0.0001; p-value <0.001). Analysis taken up for logistic regression and resulted in a 1mEq/L increase in chloride cut the odds of a prolonged stay by 53% (OR: 0.47; CI 0.26-0.85; p-value=0.012), whereas NT-proBNP, urea, and creatinine were not significant [Table/Fig-4]. These findings confirm that hypochloraemia is a strong, independent predictor of prolonged hospitalisation in ADHF, thus accepting the hypothesis.



[Table/Fig-3]: Correlation between the serum chloride at admission and length of the hospital stay.

Predictors	OR	p-value	95% CI
Serum chloride (mEq/L)	0.47	0.012	0.26 - 0.85
NT-proBNP (pg/mL)	1.00016	0.228	0.999 - 1.000
Urea (mg/dL)	0.87	0.058	0.76 - 1.00
Creatinine (mg/dL)	2.32	0.557	0.14 - 38.72

[Table/Fig-4]: Multivariate logistic regression for predictors of hospital length of stay. Multivariate logistic regression: p-value <0.05 were statistically significant and were indicated in boldface. Dependent variable is length of hospital stay.

DISCUSSION

In this prospective observational study of 60 ADHF patients demonstrated that lower admission serum chloride is a potent predictor of prolonged hospitalisation. Patients with hypochloremia experienced a mean length of stay of 13.09±1.58 days, compared to 7.75±1.97 days in the normochloremic group and 4.90±1.35 days in those with hyperchloremia (p-value<001). This present study findings were corroborated by Goyal A et al., who resulted that each 1 mEq/L rise in serum chloride reduced ADHF length of stay by 1.3% (p-value <0.003) and also align with a large cohort study showing a longer medium stay (10 days vs 9 days) in hyperchloremic acute HF patients [12,21].

In order to preserve electroneutrality, serum sodium should theoretically be reduced in tandem with another anion, such as serum chloride or bicarbonate. Recent research has shown that hypochloremia, unrelated to hyponatremia, has a significant predictive value in individuals with ADHF and chronic HF [22,23]. Chloride plays an essential role in fluid and acid-base homeostasis, tubular salt handling, and neurohormonal regulation in HF [9]. Hypochloremia is often precipitated by aggressive loop diuretic therapy or dilution that promotes RAA and vasopressin activation, impairs sodium-potassium-chloride co-transporter function in the thick ascending limb, and leads to diuretic resistance and slower decongestion [24,25]. Indeed, Hanberg JS et al., demonstrated that chloride depletion correlated with marked diuretic resistance and worse decongestive response in ADHF patients, highlighting why admission chloride measurement is often incremental prognostic insight beyond traditional markers such as sodium or BNP [24].

It is important to note that the majority of past research has focused on mortality as the primary endpoint [11,21,26,27], while only a few studies have examined duration of hospital stay [12,28,29]. However, both mortality and length of stay are indirect measures of disease severity and resource utilisation in ADHF. The post-hoc analysis of the Beta-Blocker Evaluation of Survival (BEST) trial by Ter Maaten JM et al., was the first to highlight a specific role for serum chloride in HF prognosis, as in their multivariate model, only serum chloride, rather than sodium or bicarbonate remained significantly associated with mortality, and hypochloremia portended worse survival even in the absence of hyponatremia [4].

In the present study, those with hypochloremia at admission had a mean hospital stay of 13.09±1.58 days, compared to 7.75±1.97 days in the normochloremic group and 4.90±1.35 days in those with hyperchloremia (p-value <001). Goyal A et al., first described this inverse relationship in a retrospective analysis of 167 ADHF patients, reporting median lengths of stay of 8 (IQR 6-11), and 6 (IQR 4.25-8) days across increasing chloride tertiles (p<0.011), with each 1mEq/L rise in chloride associated with a 1.3% shorter stay (95% CI: 0.5 - 2.2%; p<0.003) [12]. More recently, Hedge AA et al., confirmed these findings in another South Indian Cohort, observing median ICU stays of 17, 11, and seven days in hypochloremic, normochloremic, and hyperchloremic patients, respectively (p<0.01) [28]. Shah H et al., also reported similar findings [29]. Compared to these prior studies, this prospective design yielded a larger absolute difference over eight days between low- and high-chloride groups. This amplified effect may reflect variations in patient demographics, diuretic protocols, or discharge practices at the tertiary care centre.

Nonetheless, the consistent inverse trend across diverse populations underscores admission serum chloride as a robust predictor of hospitalisation duration in ADHF.

In the present study, serum sodium levels varied significantly across chloride tertiles (127.91±5.43 vs 131.55±6.94 vs 138.55±6.72 mEq/L; p-value=0.008) highlighting the close interplay between sodium and chloride homeostasis in ADHF. This mirrors findings from the Organised Program to Initiate Lifesaving Treatment in Hospitalised Patients with Heart Failure (OPTIMISE-HF) registry, in which hyponatremia at admission predicted both longer hospital stays, and higher in-hospital and early post-discharge mortality as each 3 mmol/L decrease in sodium corresponded to a 19.5% increased risk of in-hospital death and modest prolongation of hospitalisation [30]. However, Grodin JL et al., subsequently demonstrated that, after multivariable adjustment, only serum chloride remained independently associated with mortality and duration of stay whereas sodium lost statistical significance, underscoring that chloride adds incremental prognostic value beyond sodium alone [11].

Moreover, this study also exhibited markedly elevated NT-proBNP levels in the hypochloremia group (29005±8052 pg/mL) compared with the normochloremic (10146±7199 pg/mL) and hyperchloremic group (5668±4954 pg/mL) (p-value <0.001). This aligns with Poudel SK et al., prospective analysis, which found a moderate correlation between admission NT-proBNP and length of stay in ADHF (r-value=0.419; p-value=0.027), with higher NT-proBNP predicting stays > seven days [31]. Taken together, serum chloride and NT-proBNP constitute a complementary biomarker pair, as chloride reflects electrolyte-driven neurohormonal activation and diuretic resistance, and NT-proBNP quantifies myocardial wall stress, thereby enhancing early risk stratification and guiding decongestive therapy in ADHF.

A key strength of this study is, its prospective design with standardised Framingham-based enrollment and uniform laboratory assessment of serum electrolytes and NT-proBNP at admission, which reduced selection and measurement bias.

Limitation(s)

The single centre setting limit generalisability, and the observational nature precludes causal inference. Additionally, measured chloride only at admission without serial assessments, preventing evaluation of dynamic changes during hospitalisation.

CONCLUSION(S)

In the present study, among cohort of 60 ADHF, admission hypochloremia was linked to a significantly longer hospital stay than normo- or hyperchloremia (p-value<0.001). Low chloride remained an independent predictor after adjusting for sodium and other factors. These findings underscore the prognostic value of serum chloride alongside NT-proBNP for early risk stratification. Measuring chloride at admission is simple, cost-effective, and may guide tailored decongestive therapy. Thus, overall, admission serum chloride, combined with NT-proBNP, offers a low-cost tool to identify HF patients at risk for longer hospital stays.

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